A STUDY ON NEUROLOGICAL MANIFESTATIONS IN THYROID DISORDERS

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CERTIFICATE

This is to certify that the dissertation entitled "**A STUDY ON NEUROLOGICAL MANIFESTATIONS IN THYROID DISORDERS**" is a bonafide record of work done by **Dr.A.MARIAN JUDE VIJAY** in the Institute of Neurology, Rajiv Gandhi Government General Hospital & **MADRAS MEDICAL COLLEGE**, CHENNAI in partial fulfillment of the Tamilnadu Dr.MGR Medical University rules and regulations for the award of **D.M. (NEUROLOGY**) degree under my direct guidance and supervision during the academic year 2011-2014.

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DECLARATION

I solemnly declare that this dissertation titled "**A STUDY ON NEUROLOGICAL MANIFESTATIONS IN THYROID DISORDERS** " is done by me in the Institute of Neurology, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai under the guidance and supervision of **Prof. Dr. K. BHANU, Dip. NB., D.M.,** Professor of Neurology, Institute of Neurology, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai. This dissertation is submitted to the Tamil Nadu Dr.MGR Medical University, Chennai in partial fulfillment of the university requirements for the award of the degree of D.M. Neurology.

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CONTENTS

ABSTRACT

Introduction

Thyroid disorders both hypothyroidism and hyperthyroidism can affect the entire neuro axis resulting in various neurological manifestations.

Aim of the study

To identify the neurological manifestations of patients with thyroid disorders and to emphasize the need for thyroid screening in patients with neurological symptoms

Materials and methods

100 patients with thyroid disorders who attended Endocrinology and Neurological services at Rajiv Gandhi Govt. General hospital, Chennai, between December 2012 and February 2014 were included for the study. Patients with diabetes, renal failure, liver disorders and other chronic illness were excluded from the study**.** All patients underwent neurological examination and thyroid function tests. Selective investigations like neuro imaging, electroencephalogram, nerve conduction studies and electromyography were done according to the patient symptoms.

Results and Discussion

Total number of patients were 100 of which 50 patients were Hypothyroid and 50 patients were Hyperthyroid. The neurological manifestations observed in hypothyroidism were headache 12%, Sleep disorders 8%, cognitive decline 4%, Hashimoto's encephalopathy 4%, cerebellar involvement 2%, myeloneuropathy 2%, carpal tunnel syndrome 10%, peripheral neuropathy 10% and myopathy 2%. The neurological manifestations observed in hyperthyroidism were tremor 74%, headache 16%, Sleep disorders 8%, peripheral neuropathy 4%, myopathy 4% and thyrotoxic periodic paralysis 2%. Since it is observed from the study that thyroid disease can affect the entire neuro axis emphasizing the need for thyroid function testing. It important also important to screen for immunology testing like thyroid peroxidase antibody in selective cases and if found may need to treat with immunosuppression. On comparing neurological features associated with hypo and hyperthyroidism, the association is significantly high in hypothyroidism

Conclusion:

Thyroid disorders can affect the entire neuro axis and may present with neurological manifestations without specific symptoms and signs of thyroid dysfunction. This emphasis the need for thyroid function testing in patients presenting with neurological symptoms even without classical thyroid symptoms.

INTRODUCTION

The thyroid gland is an important endocrine gland which has actions on many systems of the body. It is located on each side of and anterior to the trachea. It is one of the largest of the endocrine glands. It weighs 15 to 20 grams in adults. The two major hormones secreted by thyroid gland are thyroxine and tri iodothyronine commonly called T_4 and T_3.

93% of hormones secreted by the thyroid gland is T_4 and only 7% is T_3.Thyroxine is believed to be a prohormone and a reservoir for the most active and main thyroid hormone T_3. T_4 is converted as required in the tissues by iodothyronine deiodinase to the more potent T_3.

There are two thyroid hormone receptor genes TRα and TRβ. Thyroid hormone exhibits its action by combining with these receptors and is mainly mediated by Tri siodothyronine(T_3). In general, energy metabolism are regulated by TRα and feedback regulation are functions of TRβ. T_3 receptor are located predominantly on neurons[1,2]. T_3 receptors in neurons mediate the effects of the hormone for neuronal cell migration and differentiation. It is well known oligodendrocytes are the principle glia of central nervous systems and schwann cells are the principle glia of peripheral nervous systems. Thyroid hormone is required for oligodendrocyte differentiation and myelination[3]. Schwann cells have been reported to express T_3 receptors which

shows the necessity of thyroid hormones for its normal functioning [4]. Hence it is well understood both central nervous system and peripheral nervous are depended on thyroid hormones for normal functioning.

Under action of thyroid hormones affecting nervous system

Thyroid hormones is necessary for the maturation of specific neurons and hence absence of these hormones during the period of active brain development leads to irreversible damage to brain causing mental retardation[5]**.**

Thyroid hormone deficiency slows metabolism, resulting in low energy expenditure, oxygen consumption, and utilization of substrates. The basal metabolic rate is reduced. Cold intolerance in hypothyroid patients is due to reduced thermogenesis.

In proportion to the drop in metabolic rate of the rest of the body the cerebral blood flow, oxygen consumption, and glucose consumption is reduced[6]. In addition to decrease in cerebral glucose metabolism there is also decrease in cerebral blood flow causing global decrease in brain activity in severe hypothyroidism[7] .

Thyroid deficiency causes myopathy due to disturbances in the mitochondrial oxidative pathway and abnormal glycogenolysis . There is change in more active fast twitching type II muscle fiber to slow twitching type I muscle fiber leading to delayed relaxation phase of ankle jerk.

Over action of thyroid hormones affecting nervous system

On the other hand increase in thyroid hormones in hyperthyroidism causes over activity of target organs and results in neurological symptoms.

Hyperthyroidism causes increase in sodium-potassium adenosine triphosphatase (Na/K-ATPase) pump activity resulting in massive shift of potassium from the extracellular into the intracellular compartment and this happens mostly in muscles leading to weakness and the condition called thyrotoxic periodic paralysis.

Hyperthyroidism is associated with myopathy. The pathogenesis of muscle dysfunction in thyrotoxicosis _is due the to direct effect of elevated level of_thyroid hormones. Thyroid hormones increase lysosomal activity causing proteolysis of muscle fibres. Thyroxine induces disturbance of oxidative phosphorylation which also leads to muscle dysfunction

Normal thyroid action but immune mediated disorder affecting nervous system

Hashimoto's encephalopathy is an autoimmune disorder. In this condition thyroid function may be hypo, hyper or euthyroid but but thyroid peroxidase antibody levels are elevated. The response to steroid and other immunomodulatory therapies suggests an autoimmune disorder.

AIM OF THE STUDY

- To assess the neurological manifestations of patients with thyroid disorders.
- To study the prevalence of various neurological manifestations in hypo/hyperthyroidism.
- To emphasize the need for thyroid screening in patients with neurological symptoms.

REVIEW OF LITERATURE

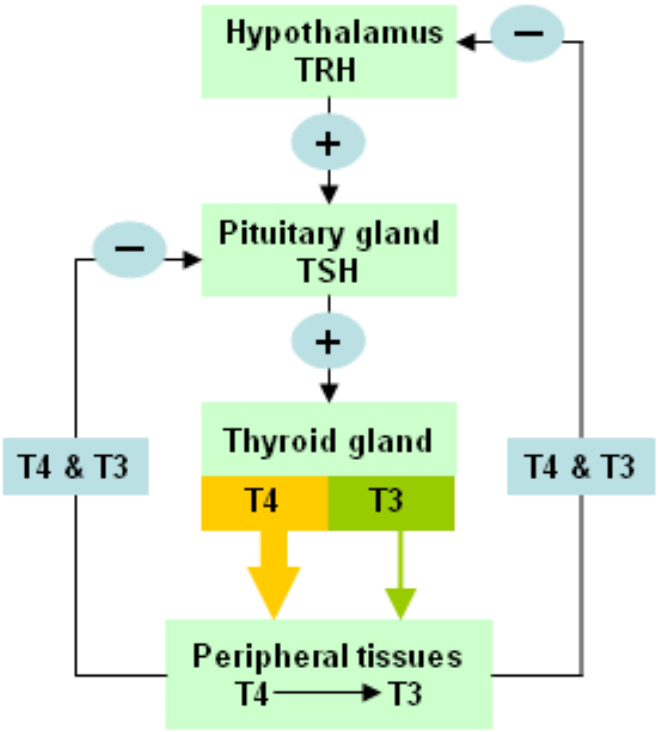
PHYSIOLOGY OF THYROID HORMONES

Thyroxin T_4 and triodothyronine T_3 are the principle hormones produced by the thyroid gland. Ingested iodine is absorbed from the gut gets converted to iodide and bound to serum albumin and transported through the blood. Thyroid gland actively extracts iodide from the circulation by **iodide trapping** mediated by sodium iodide symporter (NIS). The NIS mediated iodide transport is highly regulated, i.e., low iodide levels increases NIS and increases iodide uptake and vice versa. The trapped iodide is **oxidized** to iodine and this reactive iodine atom is added to selected thyrosyl residues in thyroglobulin (Tg) by the process called **organification** forming iodothyrosin. This iodothyrosin forms T_4 or T_3 by **coupling.** The oxidation, organification and coupling reactions are catalised by thyroid peroxidase. Thyroid hormones thus produced are bound to thyroglobulin and secreted in blood where it binds to thyroid binding globulin (TBG), Transthyritin and albumin and remaining as free hormones which is active.

CONTROL OF THYROID HORMONES

Thyroid stimulating hormone (TSH) controls the secretion of T_3 and T_4. It is secreted in a pulsatile manner by pituitary gland with peak secretion in the night. TSH secretion is stimulated by thyroid releasing hormone (TRH) which

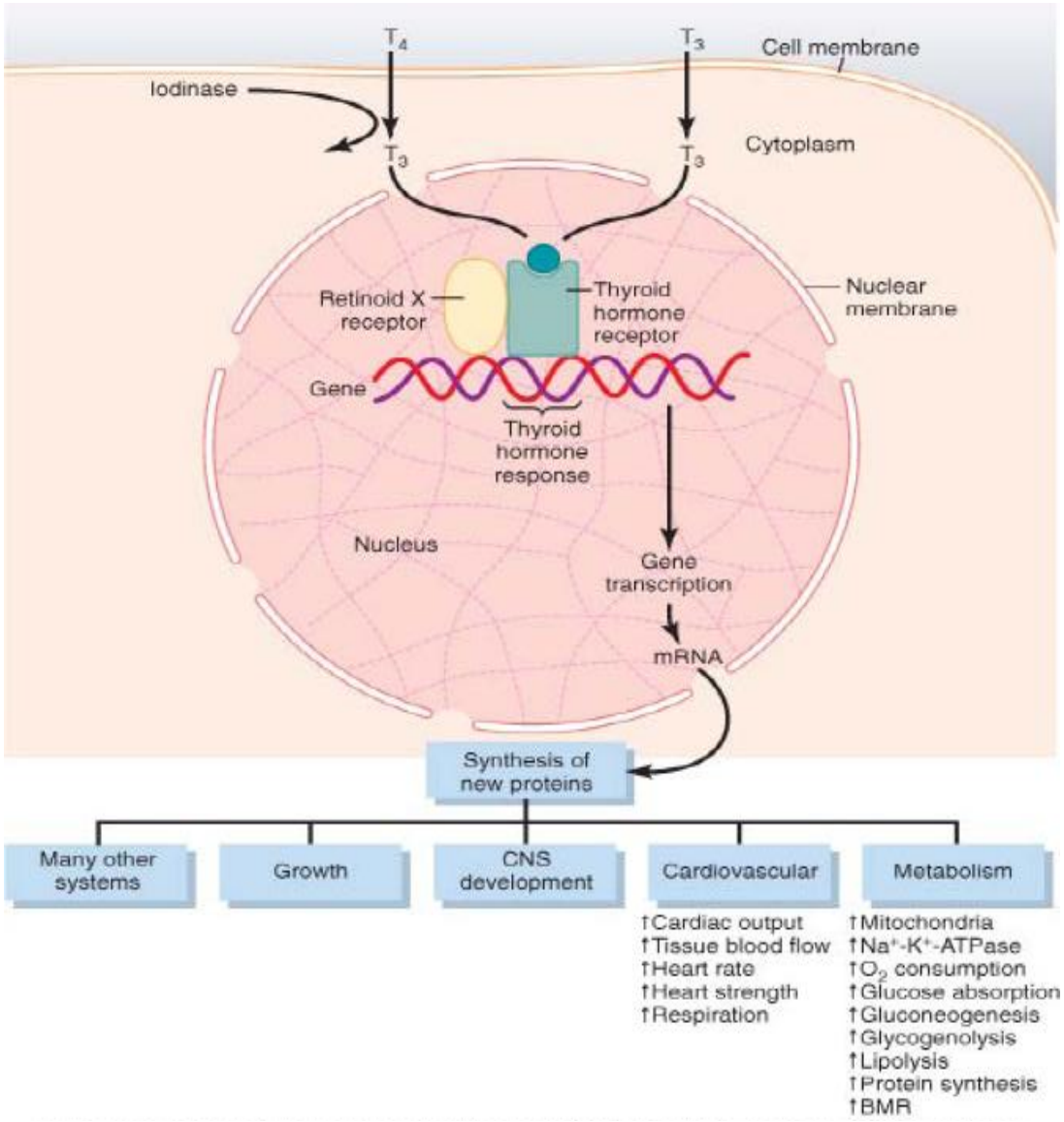
is secreted from hypothalamus. Both TRH and TSH release are under negative feedback of free T_3 and T_4.



ACTIONS OF THYROID HORMONES

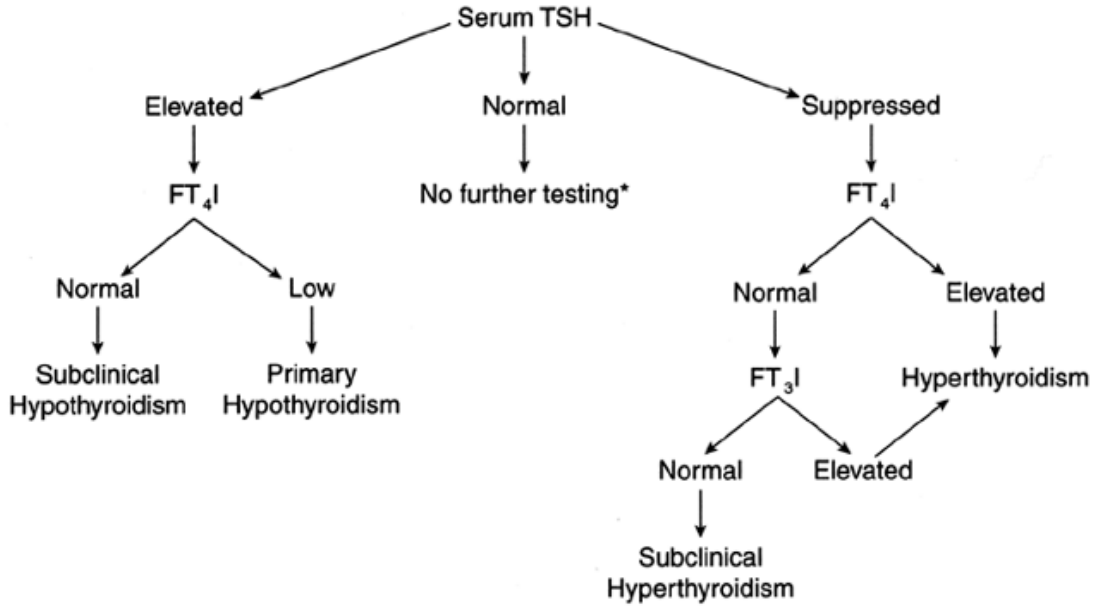
Thyroid hormones acts by binding to the nuclear thyroid hormone receptors TRα1, TRα2 and TRβ1, TRβ2. All most all tissues express TRα1, TRα2 and TRβ. But TRβ is high in pituitary, hypothalamus and is responsible for feedback control of thyroid axis. FT_3 has 10 to 15 times greater affinity than FT_4 to TRα and TRβ which explains the increased potency of free T_3. The receptor sites are mainly occupied by T_3.

Mechanism of action of Thyroid hormone at the receptor level in various systems of the body is represented in this figure.



Thyroid hormone dysfunction can affect multiple systems in the body and can present as emergency to the neurologist like hypokalemic periodic paralysis, myxedema coma or to the cardiologist like pericardial effusion, cardiac arrhythmia.

Based on the following algorithm thyroid disorders are classified as follows



In patients with immune mediated disorders thyroid function tests may be normal it is important to measure Anti Thyroid specific antibodies

In general hormone excess (hyperthyroidism) can present with some of the following symptoms and signs

- Thyroid enlargement (depending on cause)
- Pretibial myxedema (in patients with Graves' disease)
- exophthalmos, changes in visual acuity, diplopia
- Palpitations and tachycardia
- Heat intolerance or increased sweating
- Weight loss
- Alterations in appetite
- Frequent bowel movements or diarrhea
- Exertional intolerance and dyspnea

- Impaired fertility
- Nervousness and irritability
- Tremor
- Fatigue and muscle weakness
- Sudden paralysis
- Mental disturbances
- Sleep disturbances (including insomnia)

Low thyroid hormone levels(hypothyroidism) can present with some of the following symptoms an signs

- Goiter
- Fatigue
- Weight gain
- Dry skin
- Yellow skin
- cold intolerance
- Coarseness or loss of hair
- Constipation
- Irregular or heavy menses
- Infertility
- Bradycardia
- hypothermia
- Myxedema (fluid infiltration of tissue)
- Decreased concentration
- Memory and mental impairment
- Depression
- Ataxia
- Hoarseness of voice
- Muscle weakness
- Reflex delay causing delayed relaxation phase of ankle jerk

Link between thyroid hormones and neurology

The thyroid hormone receptor is a type of nuclear receptor and it is more abundant in the brain. Hence alteration in thyroid hormones leads to either

under or over activity of these receptors causing central nervous system dysfunction. The peripheral nervous system can also get affected because thyroid hormone alterations causing metabolic abnormalities of the Schwann cell. Muscle involvement can occur because thyroid dysfunction causes to metabolic disturbances in mitochondrial oxidative metabolism.

In addition to direct effect of thyroid hormone causing neurological dysfunction, immune mediated mechanisms can also operate as in Hashimoto's encephalopathy in which condition thyroid hormone levels may be normal.

Neurological manifestations of Hypothyroidism

The most common neurological symptoms of hypothyroidism are Impaired memory, slowed mental processing, depression, psychotic behavior, nerve entrapment syndromes, peripheral neuropathy, myasthenia gravis, sleep disturbances and ataxia.

Hypothyroidism and cognition

Hypothyroidism in perinatal period

Thyroid hormones is necessary for the maturation of specific neurons and hence absence of these hormones during the period of active neurogenesis leads to irreversible damage to brain causing mental retardation.

Brain-derived neurotrophic factor (BDNF) is a neurotrophin. It is most essential for the development of central nervous system and thus its function. Hence lack of thyroid hormones during early neonatal period causes reductions in mRNA and protein expression of BDNF in specific brain regions[8]. This results in impairment of normal brain development.

The target site of action of thyroid hormones are the thyroid hormone receptors. The receptors for thyroid hormone T_3 are localized in nuclei of glial cells. It is well known that the T_4 has to be converted to T_3 to exhibit the receptor mediated actions. The enzyme deiodinase type II, is mainly responsible for converting inactive T_4 to active form T_3 is also present in glial and neural cells[6]. Hence perinatal hypothyroidism results in under activations of these receptors resulting in permanent alterations of hippocampal synaptic functions leading to cognitive impairment which is moderate to severe.

Hypothyroidism in adult

It is well known that defective thyroid hormone during neonatal period affect active neurogenesis resulting in mental retardation. Even after neurogenesis, hypothyroidism in adults can cause impairment in learning abilities and memory impairment.

The adult hippocampal progenitors exhibit enhanced proliferation, survival and glial differentiation in response to thyroid hormone as

demonstrated in vitro studies in adult rat brain[9]. These results support a role for thyroid hormone in the regulation of adult hippocampal neurogenesis and raise the possibility that altered neurogenesis may contribute to the cognitive and behavioral deficits associated with adult-onset hypothyroidism

Thyroid hormones have been reported to modulate astrocyte morphology, differentiation, and proliferation and to regulate extracellular matrix organization and synthesis[10]. Thyroid hormones regulate the vimentin-GFAP (glial fibrillary acidic protein) switch, a hallmark of astrocyte differentiation, in the basal forebrain and hippocampus[10].

After thyroxine replacement, the central nervous system function usually returns to normal if the hypothyroid state was not more than 5 months in duration. But, when hypothyroid state persisted more than 7 months , there would be an incomplete recovery . This study brought out the concept of 'therapeutic window' in reversing the central nervous dysfunction caused by hypothyroidism in adult rats[11].

Insufficiency of thyroid hormones in the adulthood causes impairment of cognitive functions which is milder than during neonatal or infancy were the brain development is more. In a study that investigated whether adult-onset hypothyroidism would alter synaptic functions in the dorsal hippocampo-medial prefrontal cortex (mPFC) pathway, a neural pathway important for

learning and memory, the results suggested that alterations in synaptic plasticity of the dorsal hippocampo-mPFC pathway might contribute to understanding basic mechanisms underlying learning and memory deficits associated with adult-onset hypothyroidism[11].

Association of Headache with Hypothyroidism

Many types of headaches and migraine often found to be coexisting with hypothyroidism. The exact nature of headache in hypothyroidism is not known. It is often found a pre existing headache like migraine tend to be aggravated by the development of hypothyroidism and these headaches may show refractiveness to treatment. Hence some authors recommend to check thyroid hormones as a routine in evaluating headache. More importantly it is wise to check thyroid hormone levels in patients who has primary headache which is refractory to treatment.

Hypothyroidism and depression

Hypothyroidism can manifest with psychiatric symptoms like depression, mental retardation and even psychosis. Treatment of psychiatric symptoms alone without correction of the underlying primary cause often results in failure of treatment. Hence it is essential to look for thyroid function abnormalities in patient with psychiatric symptoms. Bipolar disorder with rapid cycling form occurs especially in women with hypothyroidism. It has

been observed certain mood abnormalities are present even in patients with subclinical hypothyroidism.

Sleep disorders in hypothyroidism

Hypothyroidism can cause abnormal sleep architecture, abnormal ventilator drive and sleep apnea[12]. The sleep apnea may be due to central causes, obstructive cause or due to both. The hypothyroid associated symptoms lethargy, somnolence and intellectual deterioration may be attributed to hypothyroid associated sleep problems in addition to direct hormonal effect. Myxedema is a reversible cause of sleep apnea and diagnostic work up for thyroid function should considered in sleep apnea.

Hashimoto's encephalopathy

Hashimoto's encephalopathy is an immune mediated disorder causing autoimmune encephalopathy characterised by high titers of anti-thyroid peroxidase antibodies[15,16]. It has been reported in all age groups pediatric, adult and elderly and is more common in females. It is characterized clinically by altered conscious state, rapid cognitive decline, myoclonus, stroke like episodes and neuropsychiatric symptoms like psychosis, hallucinations, and abulia[14]. The course of illness is relapsing and remitting. Treatment is with intravenous steroids followed by oral steroids[13]. Other immunomodulation therapy like IVIg and plasma exchange are also effective. Relapse may occur if this treatment is ceased abruptly. The treatment of steroids is continued for

months and modified according to the clinical response to treatment and monitoring the TPO antibody levels. Pathological findings can suggest an inflammatory process, but evidence of severe vasculitis are often absent. It is considered to be nonvasculitic autoimmune inflammatory meningoencephalopathies[17]. Thyroid function tests is usually normal. It is an important to consider in differential diagnosis of rapidly progressive dementia because of the reversible nature of illness with treatment.

Cerebellum and hypothyroidism

Hypothyroidism may cause slowly progressive ataxia secondary to cerebellar degeneration. There are two separate mechanisms postulated in cerebellar dysfunction in patients with thyroid disorders. It is directly due the deficiency of thyroid hormones or indirectly due to autoimmune mediated mechanism. In thyroid hormone deficient status cerebellar dysfunction could be reversed by thyroid replacement[18]. The possible mechanism could be under activity of thyroid hormone suppresses the mitochondrial function which is mostly need for purkinje fibers. In patient with autoimmune mediated cerebellar degeneration steroid remains the treatment of choice. Degenerative changes are seen in cerebellum, particularly in anterosuperior portion of the vermis, together with atrophy of ventral portion of the pons, transverse pontine fibres, and middle and superior peduncles[19]. The imaging of these patients may show midline and cerebellar hemisphere atrophy and even brain stem.

Cerebellar development during the infancy is characterise by proliferation of the external granular layer and migration of the granule cell in the molecular layer. These functions are reduced in thyroid hormone deficiencies which are mainly mediated by TRα and TRβ receptors. This is one of the best studied mechanism of receptor mediated action of thyroid hormone. The target receptor is predominantly TRβ in cerebellum ontogenesis. In one study they have found that TRβ mutant mice having severe deficit in proliferation of granule cells, arborization of purkinje cells and migration defects. Hence the target inactivation of TRβ could lead to impaired lamination and foliation leading to cerebellar atrophy inspite of normal thyroid hormone levels.

Hypothyroid effects on peripheral nervous system

Hypothyroidism can cause peripheral neuropathy . In comparison to central nervous system, the peripheral nervous system is less affected in hypothyroidism. The severity of the clinical picture of the neuropathy was more related to the duration of the disease than to the severity of the thyroid hormone deficiency. Both neurophysiological and pathological findings shows primary axonal sensorimotor polyneuropathy[23]. Study of cases of peripheral neuropathy morphologically and neurophysiologically suggest that metabolic alterations caused by endocrine disorders are responsible for the peripheral neuropathy[20]. They suggested that these metabolic alterations affect essentially

the Schwann cell inducing a segmental demyelination. Recent observations have not confirmed the previous ones. Some investigators found morphological evidence of primary axonal degeneration. In teased fibres they demonstrated arrays of myelinated ovoids in most fibres; with electron microscopy they found axonal shrinkage, disintegration of neurotubules and neurofilaments leading to axonal break down[21,22]. There is segmental demyelination secondary to axonal degeneration. Painful neuropathy due to small fiber involvement can also occur in hypothyroidism[24].

Pathophysiology may be due to deposition of mucopolysaccharide or the myxedematous tissue which leads to compression over the peripheral nerves and thereby results in swelling and degeneration of them[25].It has also been suggested that the thyroid hormones stimulate the mitochondrial respiratory activity to produce energy in the form of ATP during aerobiosis under normal physiological condition. Hormones also increase the ATPase activity and consequently Na+/K+ pump activity in this group of patients. Therefore, deficiency of ATP and reduced ATPase and decreased Na+/K+ pump activity cause subsequent alteration of pump dependent axonal transport and thereby may lead to peripheral neuropathy. Decrease glycogen degradation may also leads to energy deficit in hypothyroidism[26].

Entrapment neuropathy

Carpal Tunnel Syndrome (CTS)

The most common entrapment neuropathy associated with hypothyroidism is carpal tunnel syndrome. Carpal tunnel is the space between carpal bones and transverse carpal ligament. The median nerve passes through this space along with nine flexor tendons. The median nerve is vulnerable to compression where in conditions like edema, boney abnormalities, soft tissue swellings which increases the pressure in the carpal tunnel. It can occur in other disorders which reduce the space of carpal tunnel like rheumatoid arthritis, thickening of synovium, acromegaly, pregnancy etc.

The clinical features of CTS are parasthesias over the hand which may also extend proximally to elbow and to even shoulders. There is sensory loss over the first three digits and radial half the fourth digit. There is sparing of sensation over the thenar eminent because the palmar cutaneous nerve which supply this area arises three centimeter proximal to carpal tunnel and travels outside the carpal tunnel. There can be vasomotor changes which causes swelling, cold and shinny skin. Wasting of thenar muscle occur in advanced stages.

The electro diagnostic criteria for CTS

- Distal median motor latency >4.4ms

- Difference between distal motor latency of median and ulnar nerve >1.1ms
- Difference between distal sensory latency of median and ulnar nerve >0.2ms
- Difference between median and ulnar sensory latency on stimulating fourth digit and recording from wrist at equal distance >0.2ms
- Difference between median and radial sensory latency on stimulating thumb and recording from wrist at equal distance >0.4ms
- Palm wrist conduction:difference between median and ulnar sensory latency across 8cm > 0.4ms
- Inching technique: latency jump >0.2ms/cm
- Comparison of lumbrical (median nerve) and interosseous (ulnar nerve) latencies more than 0.6ms

Tarsal Tunnel Syndrome

Similar to CTS posterior tibial nerve can be compressed when travelling under the flexor retinaculum in the tarsal tunnel resulting in the syndrome called Tarsal Tunnel Syndrome. These patients have burning sensation, tingling and numbness of the feet aggravated by standing and walking for long distance. There may be atrophy of abductor hallucis. In electro physiological testing, the distal motor latency of the tibial nerve is prolonged. Measurement of sensory potential in the medial plantar nerve increases the diagnostic yield.

However because of myxedema associated with hypothyroidism it is difficult to test this sensory nerve. Compare to CTS in hypothyroidism Tarsal Tunnel Syndrome is rare.

Hypothyroid myopathy

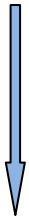
The muscular symptoms are common in hypothyroid and may range from 30-80%. The symptoms are myalgia, muscle cramps, muscle stiffness and weakness. Muscular hypertrophy reported in <10% of patients. This is a pseudo hypertrophy, the possible mechanisms being increase in connective tissues, increase in size and number of the muscle fibres and accumulation of glycosaminoglycans[27,28].The muscle weakness associated with muscle hypertrophy in adults is called Hoffman's syndrome and in childhood is called Kocher-Debre-Semelaigne syndrome. Calf muscle hypertrophy accompanies wide variety of diseases like Duchenne, Becker's muscular dystrophy and limb girdle muscular dystrophy.

On examination the deep tendon reflexes are delayed. This is pseudomyotonic reflexes where the pathophysiology is due decrease in Calcium ATPase activity secondary to under action thyroid hormones affecting fast twitching type-II of muscle fibres producing delayed relaxation of the reflex[30]. There may be myoedema in which there is mounding of muscle after light percussion[29,31].

The pathogenesis of hypothyroid myopathy is probably related deficiency of thyroid hormones causing abnormal glycogenolysis, decreased protein turn over and defective mitochondrial oxidative metabolism[22]. There is a shift of fast twitching muscle fibres to slow twitching muscle fibres. Muscle biopsies shows non specific changes with evidence of type II fibre atrophy[23].

Change in muscle fiber type due to under action of thyroid hormones

Slow twitching Type – I fiber and fast twitching Type – II fibre in muscle



Under action of thyroid hormones in hypothyroidism

Predominant slow twitching Type – I fibres

The serum creatine kinase(CK) is elevated 10 to 100 times. The serum CK does not correlate with the severity of weakness. Severity of muscle weakness is in proportion to the duration and degree of thyroid hormone deficiency. Thyroid hormone replacement therapy causes improvement in muscle power and reduction in CK level.

Myxedema coma

In patients with long-standing untreated hypothyroidism myxedema coma can occur. It often precipitated by an acute event . 80% cases are females

and occurs almost exclusively in elderly patients and occur during the month of winter.

Precipitating Factors:

- Infection like urinary tract infection and pneumonia
- Acute stress like myocardial infarction, stroke, congestive cardiac failure, surgery and trauma
- Drugs (Noncompliance with thyroid hormone replacement therapy, sedatives, tranquilizers, anesthetics, amiodarone, beta-blockers, lithium)
- Gastro intestinal bleeding
- Winter season
- Hypoglycemia

Clinical Manifestations:

The three cardinal Features of myxedema coma are altered sensorium, defective thermoregulation and a precipitating event or illness

Neurological manifestations:

It causes deterioration of mental status which may be range subtle to very severe form of coma. The subtle manifestations include apathy, cognitive impairment to more severe form like confusion, psychosis and coma. It is ideal to do mental status examination in a patients in suspected myxedema coma

since initially patient will have mild cognitive decline and only a few progress to coma.

Other signs and symptoms:

- The patient's temperature is usually less than 35.5°C (95.9°F). Many patients euthermic due to superimposed infection.
- Skin and Soft Tissue – Generalized and Periorbital edema, skin is cool and dry
- Cardiovascular manifestations like Bradycardia and Hypotension
- Respiratory system involvement causing hypoventilation with respiratory acidosis. This manifestation is mainly centrally mediated, but may be complicated by diaphragmatic muscle weakness induced by hypothyroidism.
- Gastrointestinal manifestations like constipation, abdominal distension/pain, and paralytic ileus

Diagnosis:

Diagnosis is based on exclusion of other causes of altered mental status and grossly decreased to undetectable levels of Free T_4 (and T_3).

TSH levels are grossly elevated, but it may be low in the setting of hypothalamic-pituitary disease

Blood investigation may reveal hematological abnormalities like anemia, leucopenia, metabolic abnormalities like hyponatremia, hypoglycemia, hypoxemia and elevated CK or LDH levels secondary to hypothyroid induced muscle altered membrane permeability.

Treatment

- Treatment should be initiated without waiting for laboratory confirmation of hypothyroidism

Supportive Measures

- Oxygen and mechanical ventilation if hypoventilation
- IV fluids for hypotension (caution in using pressors since this may exacerbate cardiac arrhythmias with IV thyroid replacement therapy)
- Warming room temperature and covering patients with blankets for hypothermia (avoid rapid rewarming as it is associated with peripheral dilatation and may precipitate hypotension/CV collapse)
- Hypoglycemia managed with IV dextrose infusion
- Hyponatremia may be treated with saline, fluid restriction +/- loop diuretics
- Treat precipitating factors

Thyroid Replacement

Because GI absorption is compromised, intravenous therapy is mandatory. While the necessity of intravenous thyroid hormone replacement is

apparent, some controversy exists regarding the use and dosages of levothyroxine (T_4) and liothyronine (T_3). Because of the relatively small number of patients with myxedema coma, controlled studies comparing various dosages of T_4 and T_3 are lacking. Because T_3 is more biologically active than T_4, and the conversion of T_4 to T_3 is suppressed in myxedema coma, some have advocated T_3 replacement. However, parental T_3 is not only expensive and difficult to obtain, it may also contribute to increased mortality as it causes cardiac arrhythmia.

An intravenous loading dose of 500-800 mcg of levothyroxine is followed by a daily intravenous dose of 50-100 mcg; the daily dose is administered until the patient is able to take medication by mouth. Some authorities advocate the use of additional intravenous T_3, at 10-20 mcg every 8-12 hours, especially in young patients with low cardiovascular risk.

Steroids

It is ideal to administer steroids considering the possibility of secondary hypothyroidism as in hypopituitarism where there is associated adrenal insufficiency and the possibility of adrenal crisis. Hydrocortisone 100mg sixth hourly is the treatment of choice. Cortisol level should be drawn prior to therapy, and if not depressed, the hydrocortisone can be discontinued without tapering.

Neurological manifestations of Hyperthyroidism

Hyperthyroidism can cause neurological manifestations like insomnia, seizures, encephalopathy, neuropsychiatric manifestations, thyroid associated ophthalmopathy, movement disorders like tremors, choreoathetosis, myopathy, hypokalemic periodic paralysis and myasthenia gravis.

Sleep disturbances in hyperthyroidism

Hyperthyroidism is associated with sleep disorders, the most common being insomnia. They have difficulty in initiating sleep, difficulty maintaining sleep, or waking up too early and probably related to the hyper metabolic state and anxiousness[32,33]. Due to the poor sleep during night they can have day time impairment like fatigue, concentration or memory impairment, poor school performance, mood disturbance, irritability and daytime sleepiness.

Association of Headache with Hyperthyroidism

Many types of headaches including migraine often found to be coexisting with hyperthyroidism. The exact nature of headache in hyperthyroidism is not known. It is often found a pre existing headache like migraine tend to be aggravated by the development of hyperthyroidism. Factors associated with hyperthyroidism like fatigue, perspiration, anxiety, decreased sleep, rapid beating of heart and changes in menstrual cycle aggravate the pre existing headache. Thyroid problem are more prevalent in women. It has been suggested the estrogen levels are high in patients suffering

from hyperthyroidism affecting the hormonal balance, thus causing menstrual irregularity. This increased estrogen level could play a role in the causation of headache in women. Hence it is ideal to check patients with refractory primary headache for thyroid abnormalities.

Psychiatric Manifestations of Hyperthyroidism

Hyperthyroidism can cause various psychiatric manifestations like depression, anxiety[34], panic disorders[36], psychosis[37] and bipolar disorders[39]. Treatment of hyperthyroidism results in improvement of symptoms in parallel to the improvement in hyperthyroid symptoms[38]. But some patients need anti psychiatric drugs due to the persistence of psychiatric symptoms remaining after ameliorations of hyperthyroidism.

Encephalopathy in hyperthyroidism

These clinical manifestations are seen in Hashimoto's encephalopathy which is due to autoimmune etiology where the patient may be hyper or hypo or euthyroid. The possible mechanism of nonvasculitic autoimmune inflammatory meningoencephalopathies is attributed as already mentioned.

Thyroid-associated ophthalmopathy (TAO).

It is an inflammatory disease involving the orbital tissues[39]. The inflammation is cytokine mediated and this results in proliferation of fibroblast, increased deposition of extracellular matrix, proliferation of

adipocytes. There is edema, inflammation and fibrosis causing of restriction of extra ocular muscle movement.

There are 3 main subtypes of TAO: congestive ophthalmopathy, ocular myopathy, and a mixed form.

Congestive ophthalmopathy

It is characterized by inflammation of the orbital connective tissue, with relative sparing of the extra ocular muscles and manifests clinically with eye swelling, conjunctival injection, chemosis, watery or gritty eyes, and exophthalmos.

Ocular myopathy

It is characterized by inflammation and swelling of the extraocular muscles, and manifests as ophthalmoparesis, diplopia, and occasionally painful eye movements.

Mixed congestive and myopathic ophthalmopathy

It is the most common presentation.

Thyroid-Associated Ophthalmopathy Grading System

Grade		Clinical findings
0	-	**N**o symptoms or signs
1	-	**O**nly signs-Lid lag, stare, upper eyelid retraction
2	-	**S**oft tissue involvement-Eyelid or conjunctival swelling
3	-	**P**roptosis
4	-	**E**xtraocular muscle involvement
5	-	**C**orneal ulceration
6	-	**S**ight loss- Compressive optic neuropathy

Mnemonic : **“NO SPECS”**

Neuromuscular junction disorders

Myasthenia gravis may be seen in a proportion of patients with hyperthyroidism(Graves disease)[41,42]. Patients with myasthenia gravis have an increased incidence of thyroid disorders; and 5 to 10% of myasthenic patients are hyperthyroid[40,43]. The coexistence of the two conditions is probably due to the underlying genetic predisposition to autoimmune disease

Hyperthyroid myopathy

Myopathy associated with hyperthyroidism can be acute and chronic thyrotoxic myopathy.

Acute thyrotoxic myopathy

Acute thyrotoxic myopathy appears within days of onset of thyrotoxicosis. This is due to the rapid degradation of the muscle fibers. It is usually associated with severe muscle cramps and muscle pain. It can also cause weakness of respiratory muscle resulting in respiratory failure. Rapid course with rhabdomyolysis, myoglobinuria, and renal failure may occur with severe thyrotoxicosis

Chronic thyrotoxic myopathy

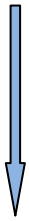
Muscle symptoms usually appear 6 months after the onset of thyrotoxicosis. Myalgias, fatigue, and poor exercise tolerance are common presenting symptoms. It is a slowly progressive illness which preferentially affects pelvic girdle and thigh muscles. Most importantly despite the muscle

weakness and wasting, serum creatine kinase remains normal in contrast to hypothyroid induced myopathy.

In contrast to hypothyroid myopathy where there is type I slow twitching fibers predominance, in hyperthyroid myopathy there is predominance of fast twitching type II fibers on histopathological examination. The pathogenesis of muscle disfunction is due the increased thyroid hormone levels causing disturbances in oxidative phosphorylation[44]. The thyroid hormone also increases the lysosomal activity leading to distruction of muscle fibers[45]. There is muscle atrophy due to the increased protein catabolism.

Change in muscle fibre type due to over action of thyroid hormones[26]

Slow twitching Type – I fibre and fast twitching Type – II fibre in muscle



Overaction of thyroid hormones in hyperthyroidism

Predominant fast twitching Type – II fibres

Thyrotoxic Periodic Paralysis (TPP)

TPP is an alarming and potentially lethal complication of hyperthyroidism characterized by muscle paralysis and hypokalemia due to a massive intracellular shift of potassium[46]. This condition mainly affects male patients of Asian descent. Many affected patients do not have obvious

symptoms and signs of hyperthyroidism. Hence it is necessary to check TFT in patients presenting with TPP even without signs and symptoms of hyperthyroidism.

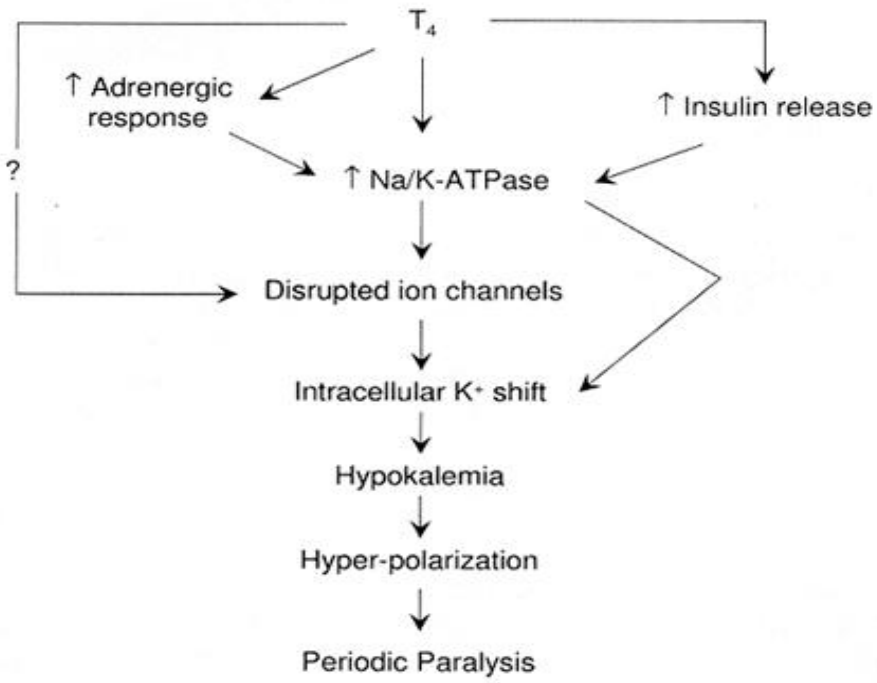
Pathogenesis of TPP

Hypokalemia in TPP is the consequence of a rapid and massive shift of potassium from the extracellular into the intracellular compartment,mainly into the muscles. This is believed to be related to increased sodium-potassium adenosine triphosphatase (Na/K-ATPase) pump activity. Overall, the data revealed an increased number as well as activity of the Na/K-ATPase pump in patients with thyrotoxicosis. Patients with TPP had significantly higher pump activity than thyrotoxic patients without TPP. When thyrotoxicosis was controlled, Na/K-ATPase activity returned to a level similar to that of healthy controls.Thyroid hormones can increase Na/K-ATPase activity in skeletal muscle, liver, and kidney to induce an influx of potassium into the intracellular space . Among the various Na/K-ATPase subunits, the α1-, α2-, β1-, β2-, and β4-subunits are expressed in skeletal muscles .Thyroid hormone-responsive elements are present in the upstream region of these five genes, and thyroid hormones has been shown to increase Na/K-ATPase activity via both transcriptional and posttranscriptional mechanisms. Apart from direct stimulation by thyroid hormones, catecholamine can also increase Na/KATPase activity in skeletal muscle .The enhanced β-adrenergic response

in thyrotoxicosis further increases Na/K-ATPase activity and may explain why nonselective β-adrenergic blockers can abort or prevent paralytic attacks.

In addition to an increased adrenergic response, patients with TPP have an exaggerated insulin response during oral glucose challenge, compared with thyrotoxic patients without TPP. Insulin-response sequences are present in the upstream region of Na/KATPase genes in patient with TPP and insulin has been shown to stimulate Na/K-ATPase activity. Hence,insulin can play a permissive role for the potassium shift in patients with TPP. The hyperinsulinemic response may explain the association of TPP with carbohydrate-rich meals and sweet snacks. Exercise releases potassium from the skeletal muscles, whereas rest promotes influx of potassium. This explains why paralytic attacks occur only during recovery from exercise and resumption of exercise can abort an attack .

Only a few patients who have thyrotoxicosis develop TPP and not all. Hence this raise the possibility of genetically associated predisposition of Na/K-ATPase activity either directly by the thyroid hormone or indirectly via increased adrenergic response. The human leukocyte antigen (HLA) B46, DR9, and DQB1*0303 have been reported to be present at a higher prevalence among Hong Kong and Chinese TPP patients, whereas HLA A2, BW22, AW19, B17, and DRW8 are reported to be associated in Singapore, Chinese and Japanese, respectively



Differential diagnosis of hypokalemic paralysis:

Type of potassium imbalance could be due to transcellular shift or potassium loss.

Transcellular shift :

IV insulin, Thyrotoxic periodic paralysis, Familial periodic paralysis, Sporadic periodic paralysis.

Potassium loss:

Renal loss of potassium- Bartter's syndrome, Gitelman's syndrome, Renal tubular acidosis.

Gastrointestinal loss of potassium- diarrhoea, vomiting

Where the potassium loss is obvious due to GI causes like vomiting, diarsrhoea, it is difficult identify renal causes unless properly investigated. The urine potassium–creatinine ratio and transtubular potassium gradient (TTKG) are useful indices to diagnose hypokalemia secondary to renal loss. The TTKG is a semiquantitative index of the activity of the potassium secretory process, calculated by [urine K ÷ (urine osmolality/plasma osmolality)] ÷ plasma K.

It is very important in understanding the pathogenesis when treating. When the hypokalemia is due to pottasium loss it is ideal to correct potassium loss according to the deficit. But in managing hypokalemia were the pottasium loss is apparent than real as in TTP there is danger of rebound hyperkalemia when the trans cellular shift reverses[47].

Management

Management can be divided into immediate correction of hypokalemia and treatment of the underlying disorder.

Correction of Hypokalemia:

The hypokalemia in TPP is due to the shift if potassium from extra cellular compartment into the intra cellular compartment due to the over action of Na/K ATPase pump. It is an apparent hypokalemia and not due the real loss of potassium from the body. There is a positive correlation between the dose

of potassium administered and the degree of rebound hyperkalemia during treatment. Potassium can be given intravenously or orally to hasten muscle recovery and prevent cardio vascular complications. Rebound hyperkalemia occurred in 40% of patients who received >90 mEq of potassium chloride within the first 24hours[35]. Patients receiving a total dose of ≤50 mEq of potassium chloride rarely develop rebound hyperkalemia. Lower doses of potassium chloride may be effective while lowering the patient's risk of hyperkalemia.

A non selective beta-blocker (propranolol) normalizes the serum potassium level within hours. Hence in addition to treatment with potassium the initial treatment should also include propranolol[49-52].The mechanism of action of propranolol is by blunting the hyper adrenergic stimulation of Na/K ATPase thus preventing the intra cellular shift of potassium[48].

Treatment of the underlying disorder:

The primary therapy for TPP is the treatment for hyperthyroidism. To prevent the recurrence of TPP patients should avoid the precipitating factors and continue propranolol till euthyroid state is reached[53]. TPP is curable when the thyroid hormone normalizes with treatment.

Tremor in Hyperthyroidism

Tremor occurs in most patients of thyrotoxicosis. Reflex oscillation elicited by afferent muscle spindles pathway is responsible for tremor in hyperthyroidism rather than involvement of central oscillator like inferior olive, basal ganglia and thalamus. This mechanism is probably by enhancement of physiological tremor associated with enhanced sympathetic activity due over activity of thyroid hormones. The tremor disappears with treatment of hypothyroidism.

Hyperthyroidism-associated chorea

Hyperthyroid disorder can occasionally give rise to chorea[55]. Most often chorea occurs bilateral but sometimes occurs unilaterally. The pathology is often related to increased response of striatal dopamine receptors to dopamine suggesting the possibility of hyperthyroid status induced increased sensitivity of dopamine receptors[56]. This is one of the examples of increase receptor site sensitivity in brain without a structure lesion. Chorea disappears with treatment when the thyroid function returns to normal level. This also suggest the possibility of specific effects of thyroid hormone on the neuro transmitter system.

MATERIALS AND METHODS

With the aim of studying the neurological manifestations in patients with thyroid disorders this study was done in Madras Medical College & Rajiv Gandhi Government General hospital over a period of 15 months between December 2012 to February 2014.

Methodology

To examine the patient attending endocrine op with thyroid dysfunction and who had neurological complaints and subject the patient for further investigations like blood testing, imaging, electroencephalogram and nerve conduction studies according to patients symptoms.

Patient attending neurology op and patient admitted in neurology ward were tested with thyroid function test if hyper/hypothyroidism suspected.

Blood investigations

Routine blood test include complete blood count, Renal function test, serum electrolytes, Liver function test, lipid profile, Elisa test for HIV and VDRL.

Thyroid function test

Blood test to asses thyroid function include Thyroid-stimulating hormone (TSH), Free and Total Thyroxine (T_4), Free and Total Triiodothyronine (T_3), Thyroid peroxidase antibody (TPO**)**, TSH receptor antibodies (TRAb) and Thyroid stimulating antibodies (TSI/TSIAb)

Imaging of brain with CT/MRI

For those patients who have seizures, cognitive decline and other central nervous system manifestation

Electroencephalogram

For patients with seizures

Nerve conduction studies

For those patients with entrapment syndrome, peripheral neuropathy and other peripheral nervous system manifestation

Electromyography

For those with suspected myopathy

Exclusion criteria

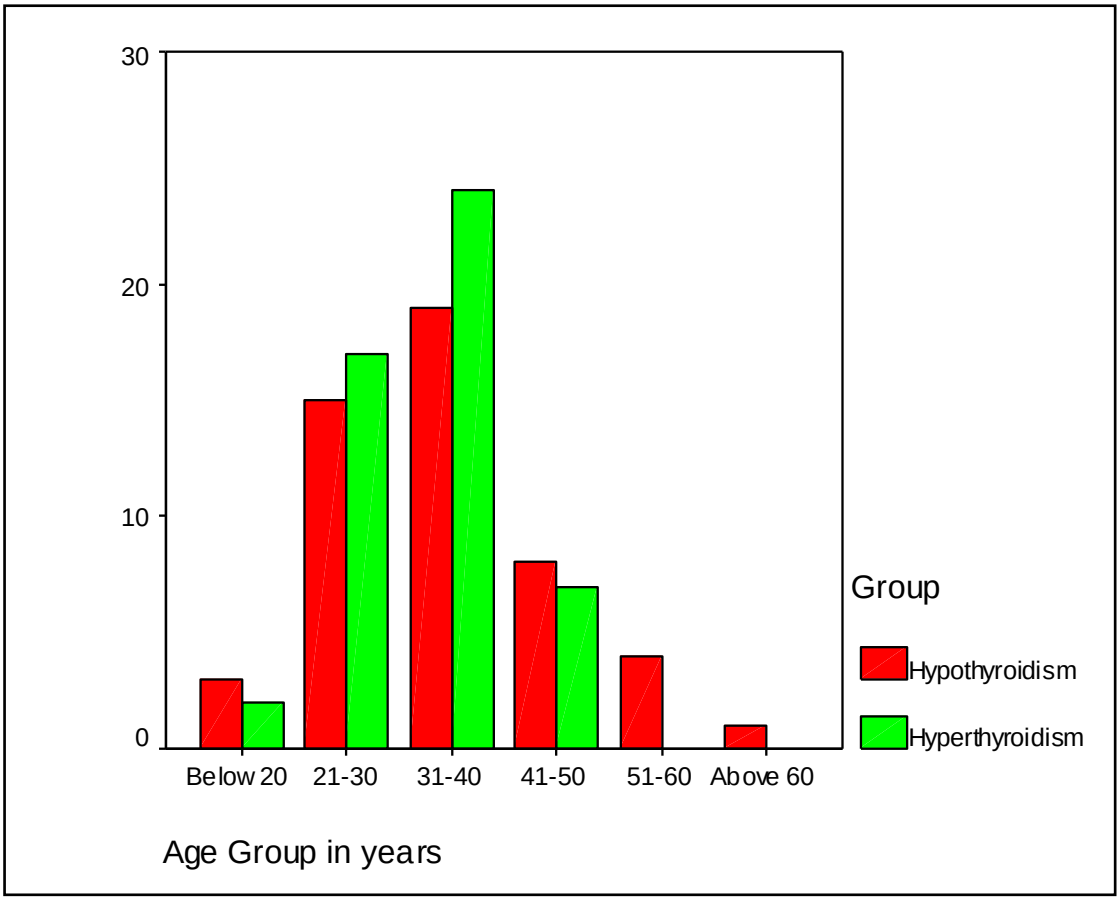
Chronic illness like diabetes mellitus, chronic renal failure, liver disease, malignancy, HIV infection are excluded from the study.

Specific other diseases which could also accounted for the neurological manifestation are excluded like

- Excluding CNS infection in suspected Hashimoto's encephalopathy.
- Excluding CNS lesions by imaging in seizure disorder.
- Excluding diabetes/chronic alcoholism in peripheral neuropathy.
- Excluding hereditary, inflammatory and other causes in myopathy.

RESULTS AND OBSERVATIONS

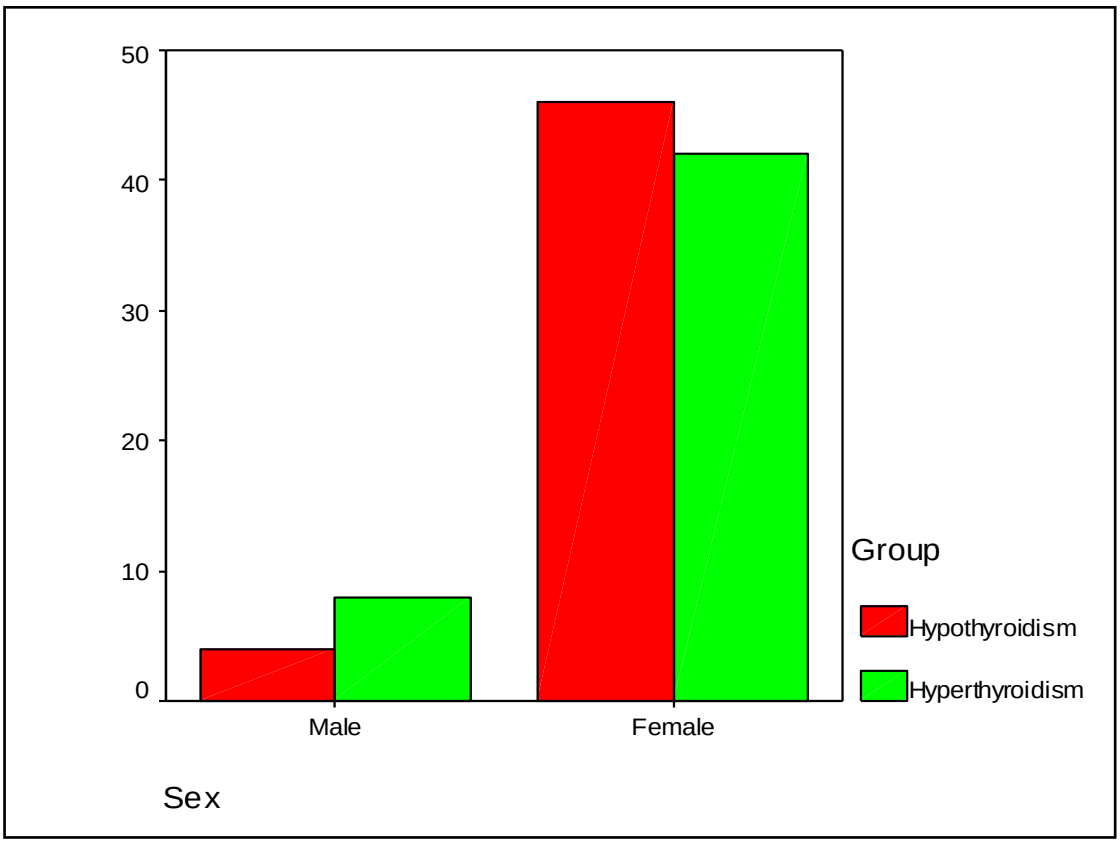
In this study 100 patients with thyroid disorders were analysed for neurological manifestations, in which 50 patients were hypothyroid and 50 patients were hyperthyroid



Descriptive Statistics

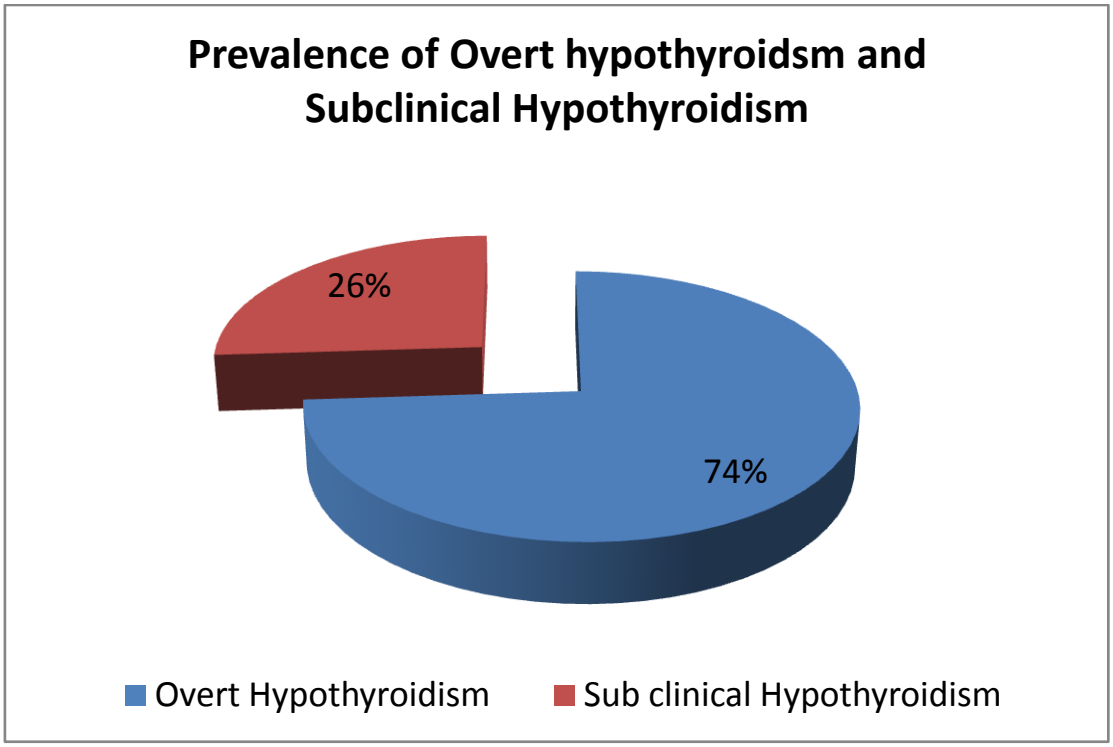
	N	Minimum	Maximum	Mean	Std. Deviation
Age in years	100	14	72	34.62	9.927

Sex distribution of Hypo and Hyperthyroidism

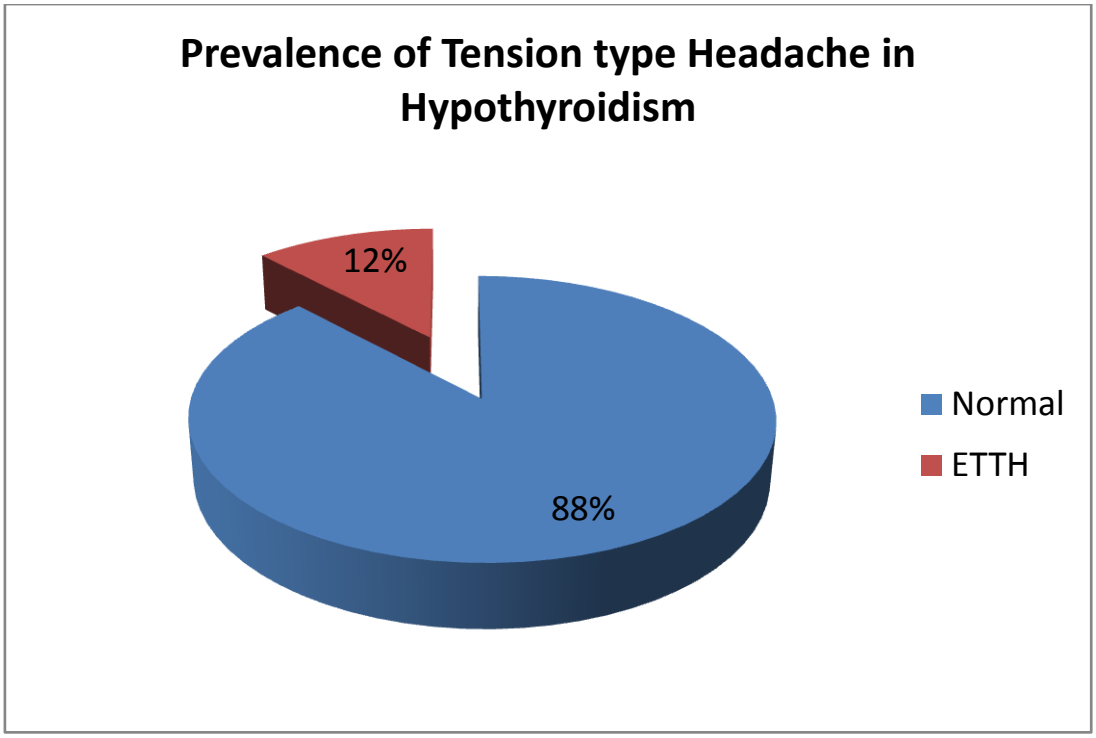


Sex * Group Crosstabulation

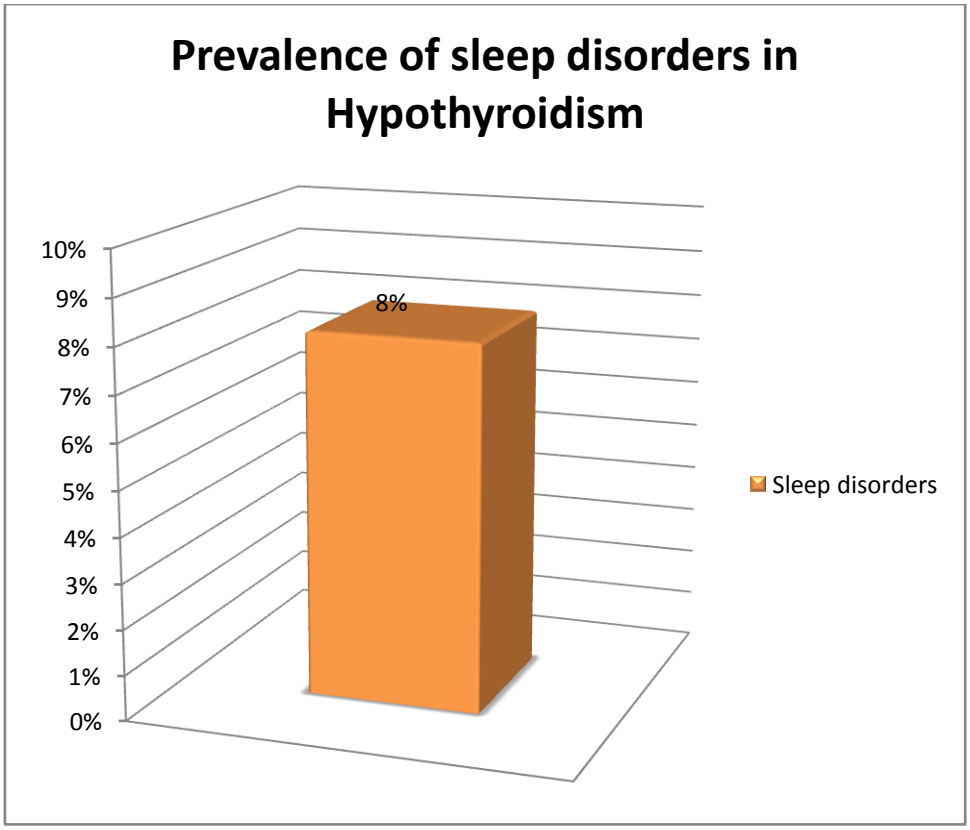
			Group		Total
			Hypo-thyroidism	Hyper-thyroidism	
Sex	Male	Count	4	8	12
		% within Sex	33.3%	66.7%	100.0%
		% within Group	8.0%	16.0%	12.0%
	Female	Count	46	42	88
		% within Sex	52.3%	47.7%	100.0%
		% within Group	92.0%	84.0%	88.0%
Total		Count	50	50	100
		% within Sex	50.0%	50.0%	100.0%
		% within Group	100.0%	100.0%	100.0%



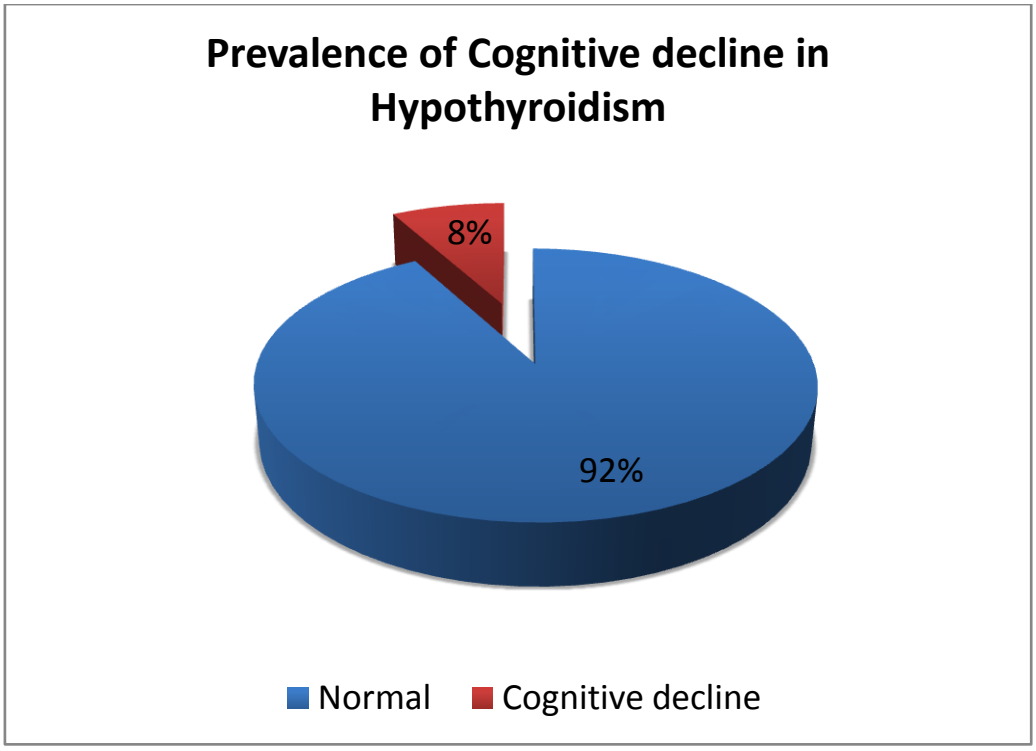
The patients with elevated TSH and low levels of thyroxine are grouped under overt hypothyroidism. Patients with elevated TSH alone with normal levels of thyroxine are grouped under subclinical hypothyroidism.



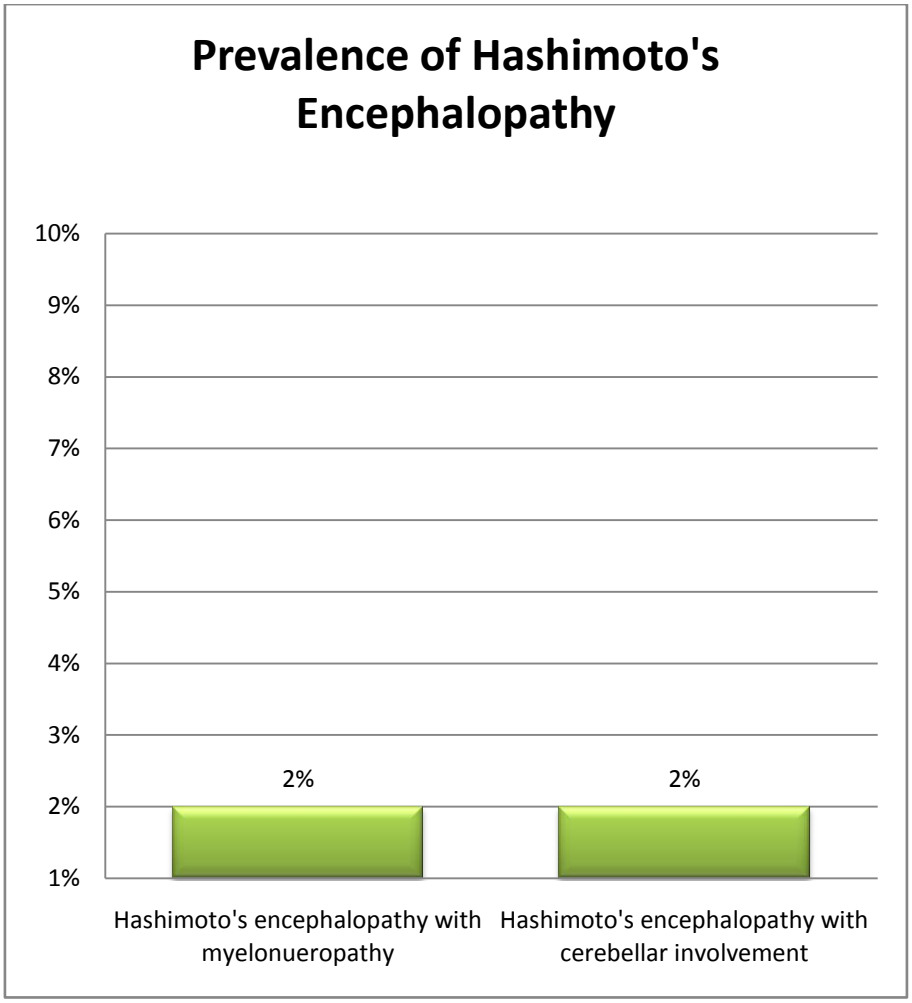
In hypothyroidism 12% of patients had headache which is of tension type headache and it was episodic in nature. Hence we compared with other studies which estimated the prevalence of headache in the general population to know whether the association between hypothyroidism and headache is significant or not[57].



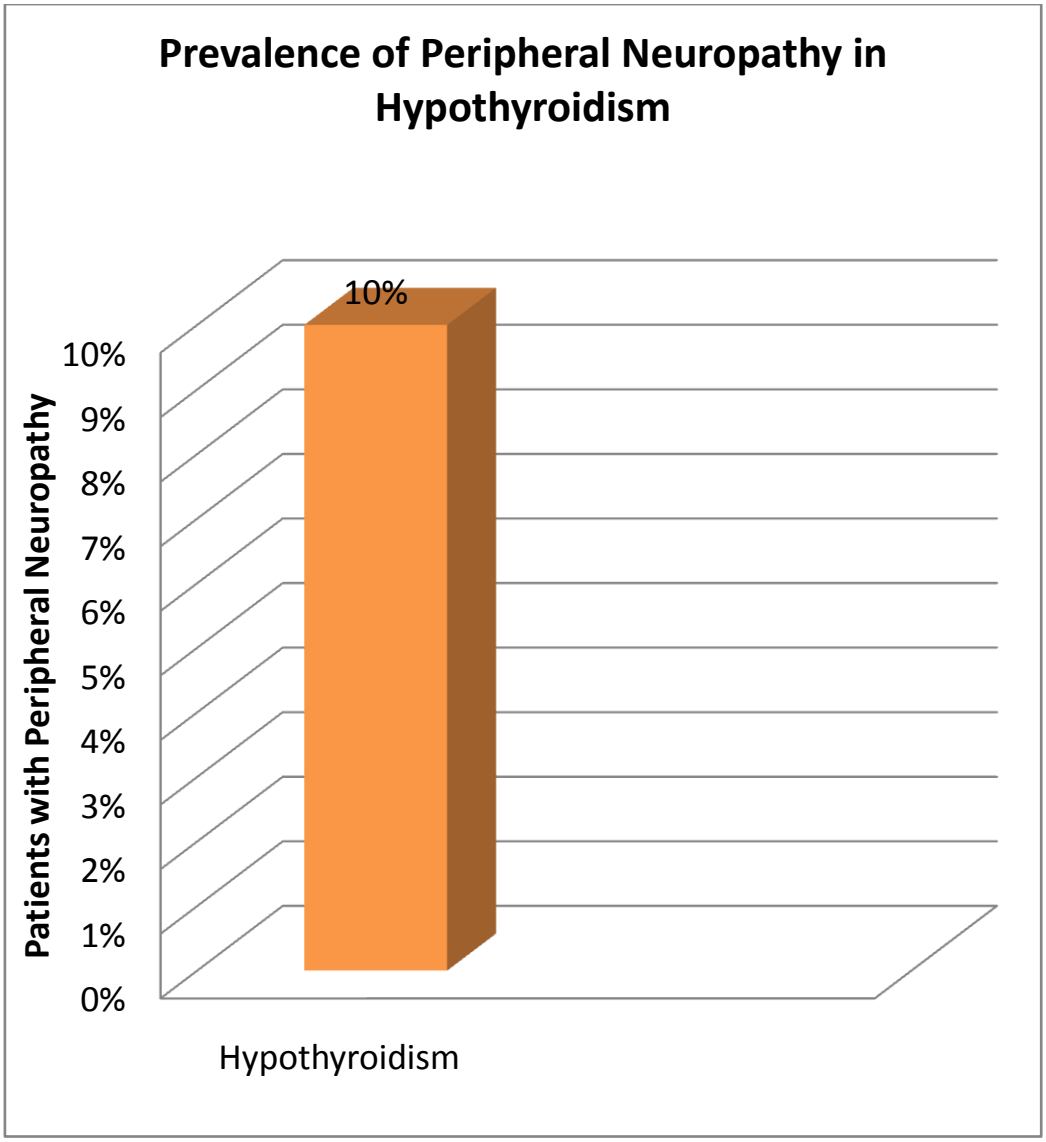
Patients with sleep disorders in hypothyroidism is 8%. Most of the patients had complaints of increased sleepiness despite adequate night time sleep. Only one patient had insomnia in the form of difficulty in initiating sleep.



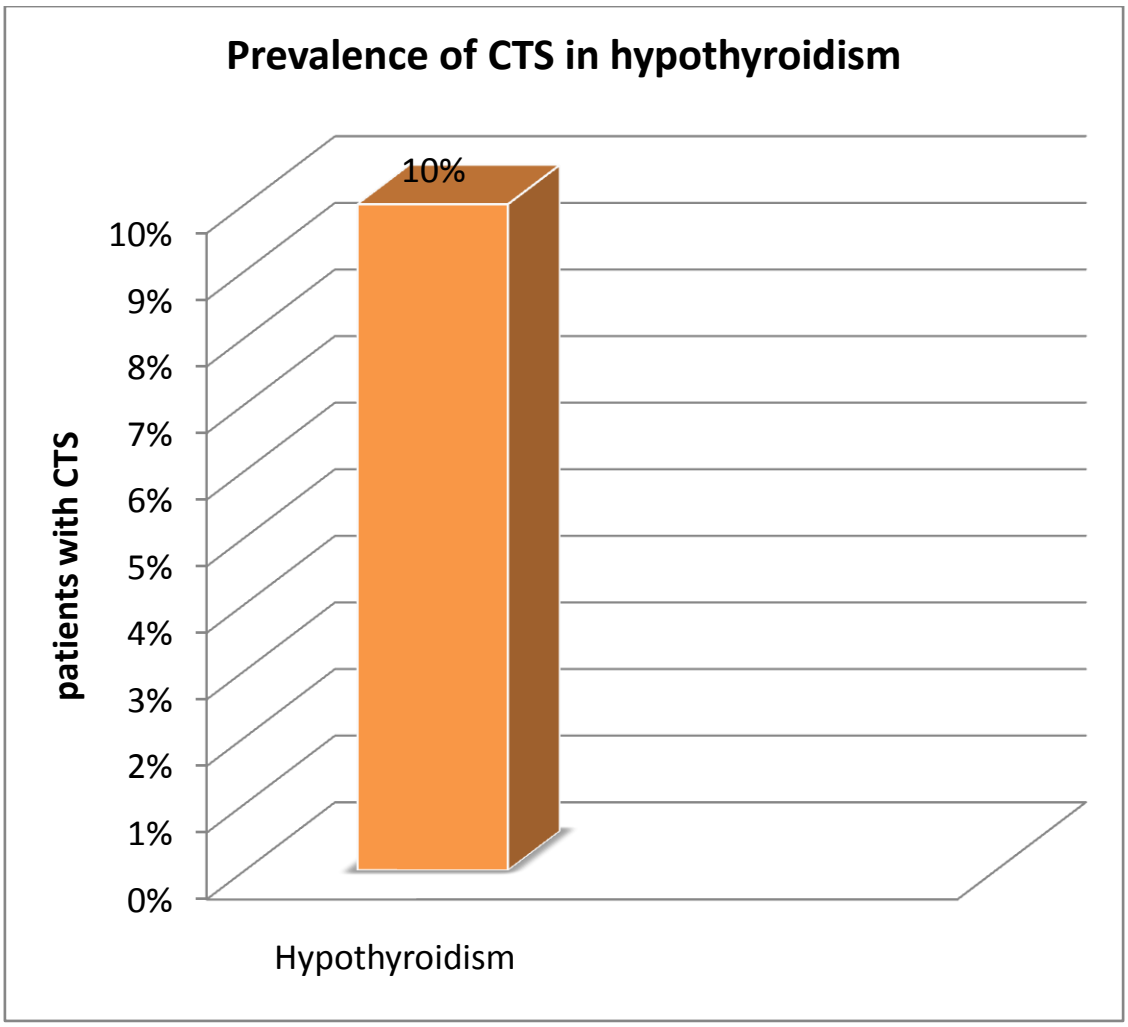
It is well known that hypothyroidism during infancy causes severe cognitive impairment. Adult onset hypothyroidism also causes cognitive impairment, but of lesser severity. Here 8% adult hypothyroid patients had cognitive decline. Of these patients, 4% had Hashimoto's associated encephalopathy mediated cognitive decline which is a part of autoimmune encephalitis. Hence the patient having decrease in cognitive function which is directly due to under action of thyroid hormone is 4%.



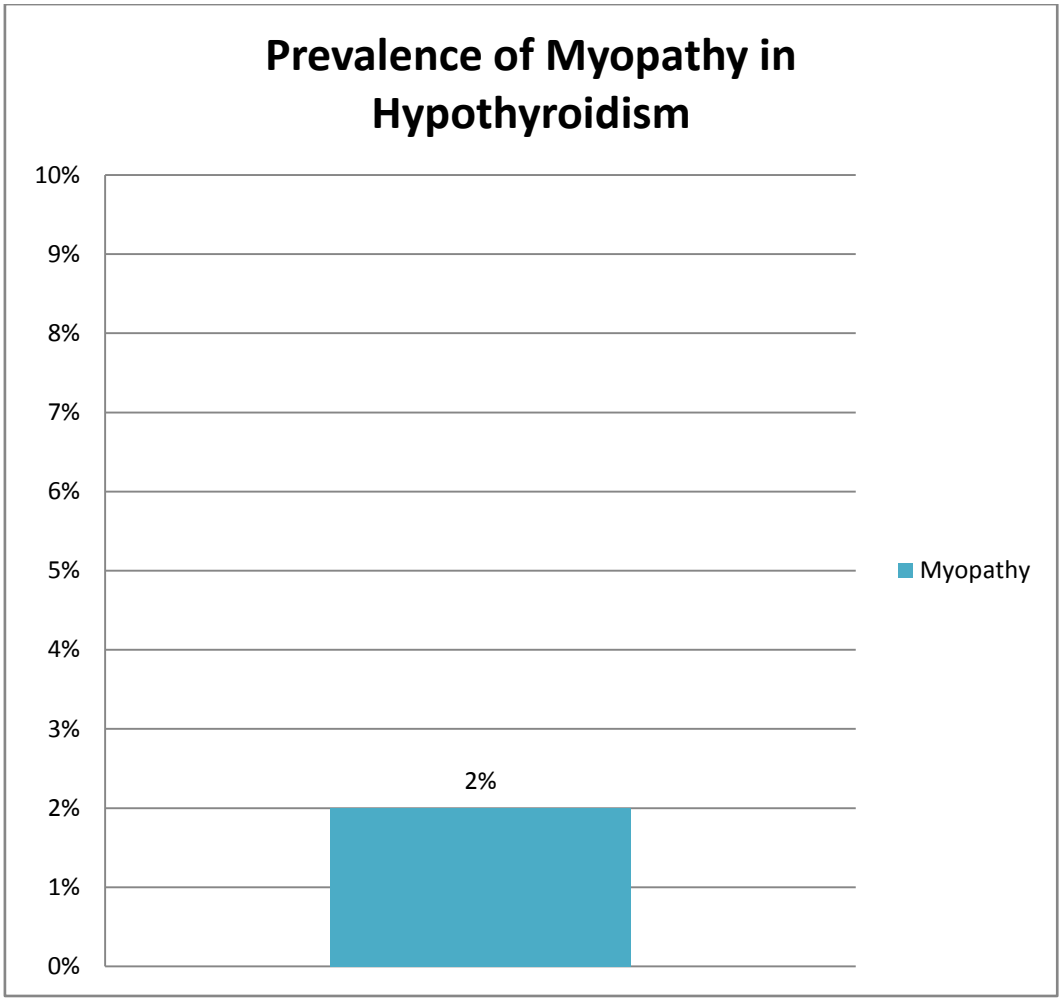
Hashimoto's encephalopathy is diagnosed after exclusion of other causes which could account for the same symptoms and signs and high titers of TPO antibodies. Here we like to highlight the immune mediated mechanism operating causing encephalopathy in both cases, but the same mechanism causing myelopathy in one patient and cerebellar involvement in another patient.



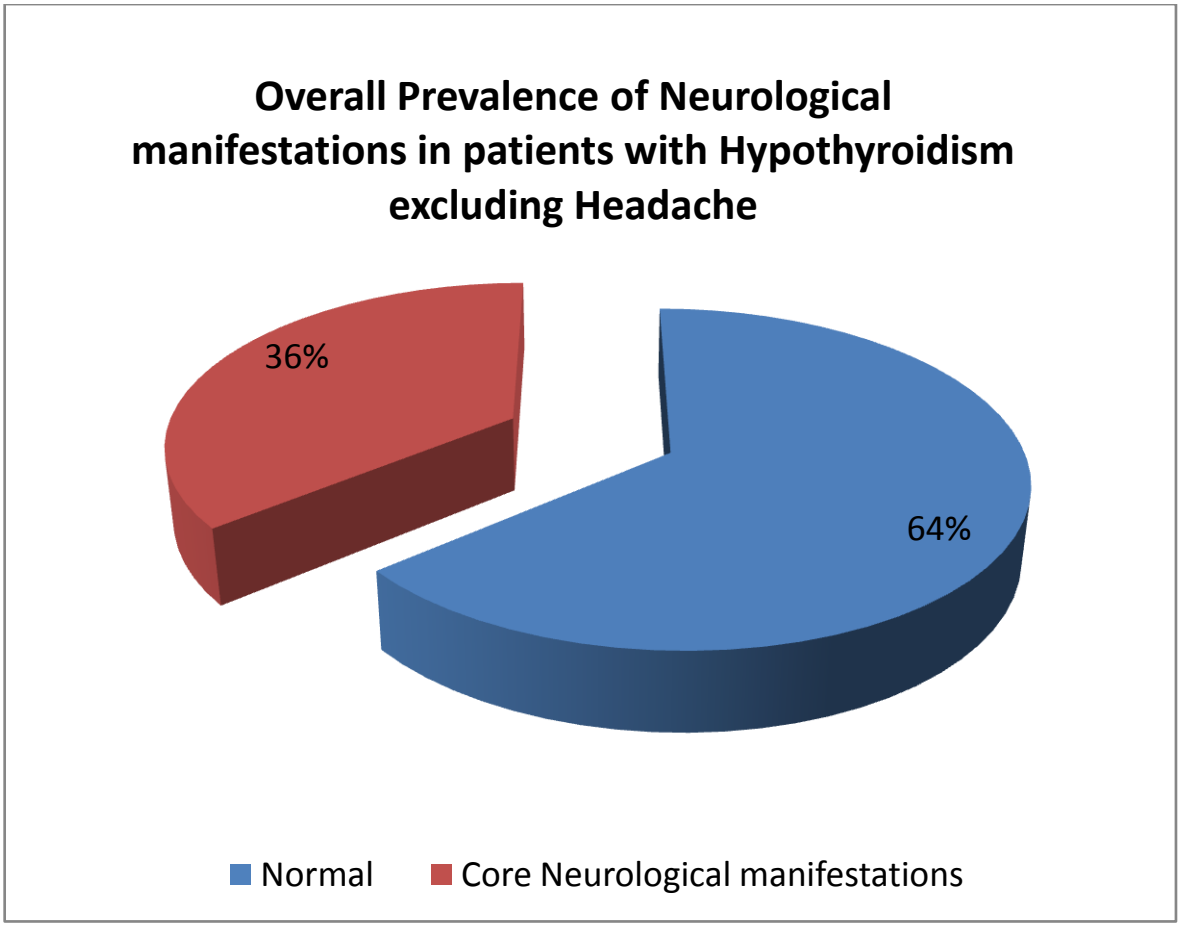
10% of the population in the study group have peripheral neuropathy. It was also observed patients in overt hypothyroidism are more affected than in subclinical hypothyroidism. Only one patient in subclinical hypothyroidism had peripheral neuropathy. This patient was diagnosed as Hashimoto's encephalitis and hence the possibility of immune mediated mechanism causing peripheral neuropathy considered.



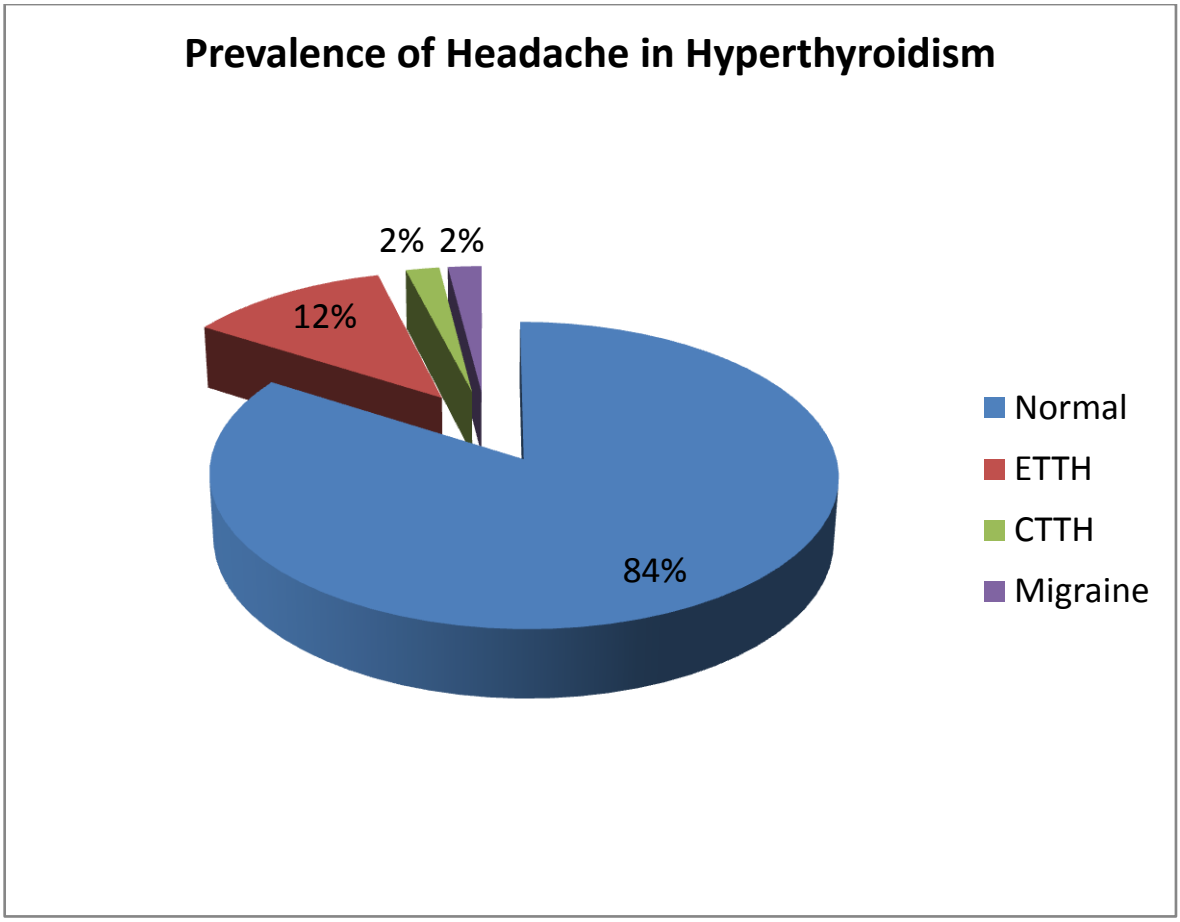
The prevalence of carpal Tunnel syndrome in hypothyroidism is 10%. On comparing the prevalence of CTS in overt and subclinical hypothyroidism it is more associated with overt hypothyroidism.



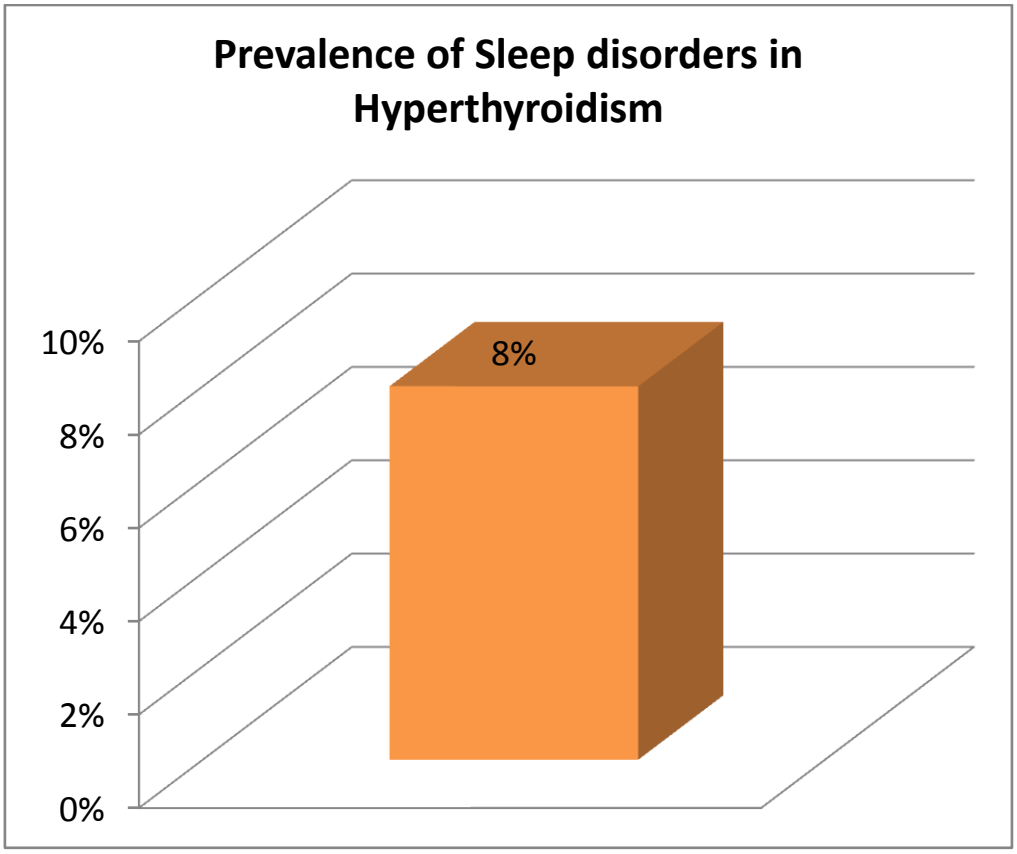
Only 2% of hypothyroid patients had myopathy and the weakness was mild as assessed by MRC grading is ≥4.



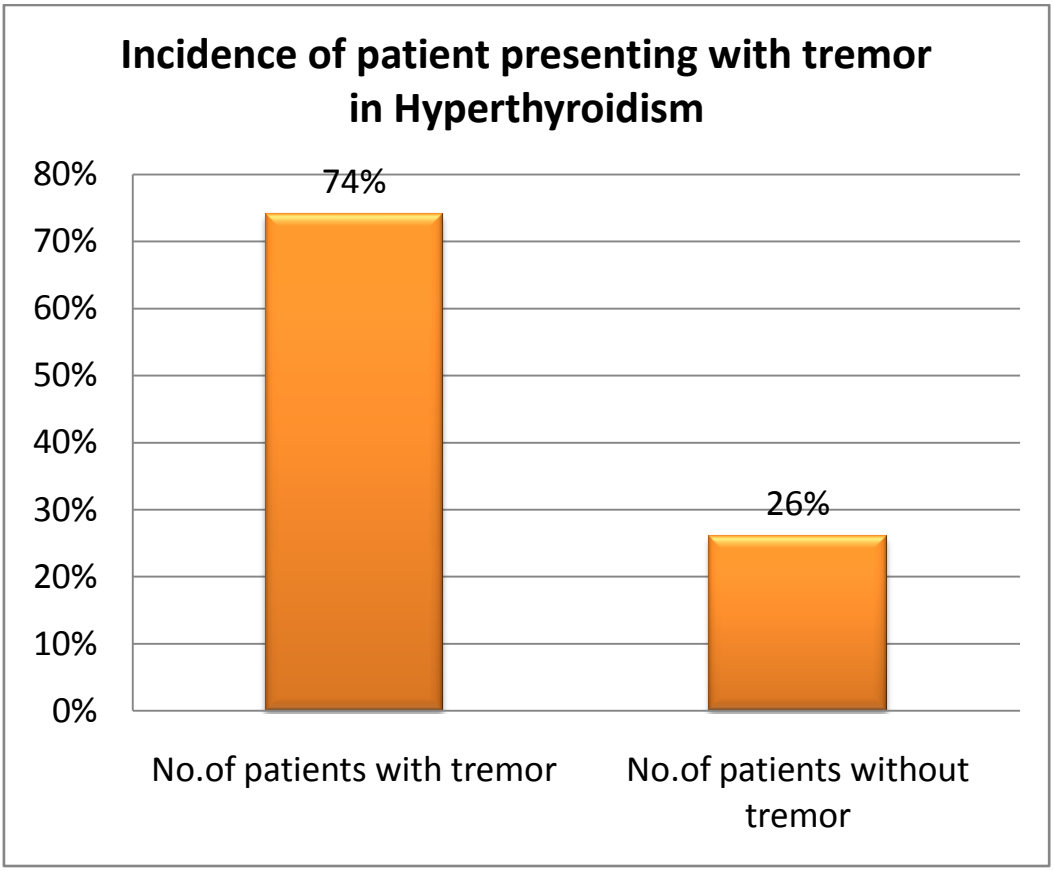
After excluding less serious and other illness like headache where the association is mere a coincidence, the number of population with core neurological manifestations in our study is 36%.



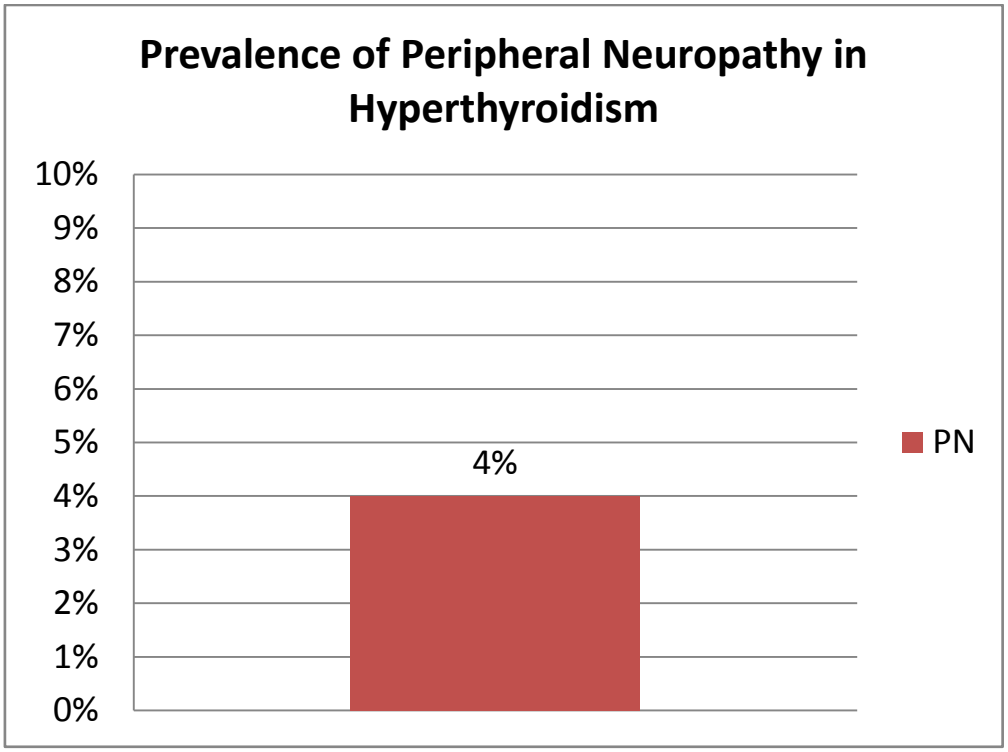
16% of patients with hyperthyroidism had headache. Of these, 12% had episodic tension type headache(ETTH), 2% had chronic tension type headache(CTTH) and 2% had migraine. The prevalence of tension type headache and migraine it is no more greater than in general population when compared to previous studies[57].



Patient with sleep disorders in hyperthyroidism is 8%. All the patients had complaints of decrease in duration of sleep and difficulty in initiating sleep.



Most patient in hyperthyroidism presents with tremulousness of hands. In our study 74% of patients had tremor initially, which disappears with treatment as thyroxine level normalizes.



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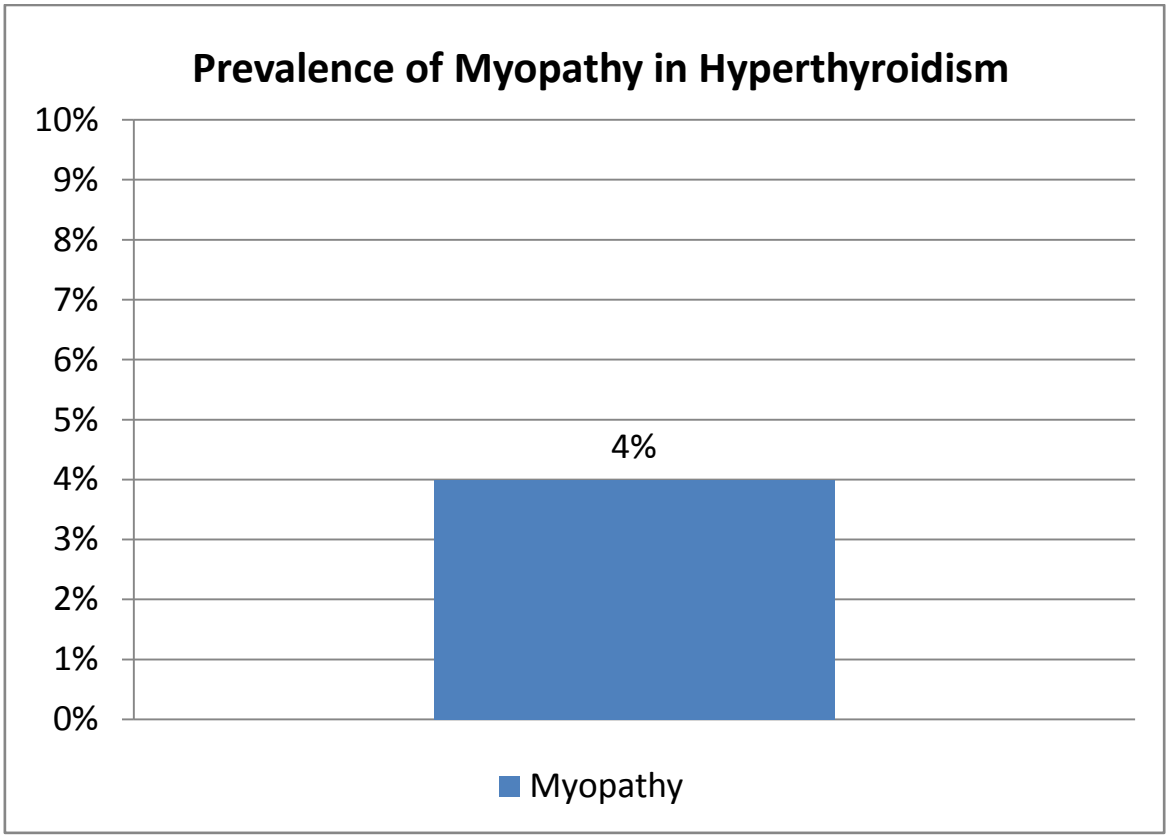
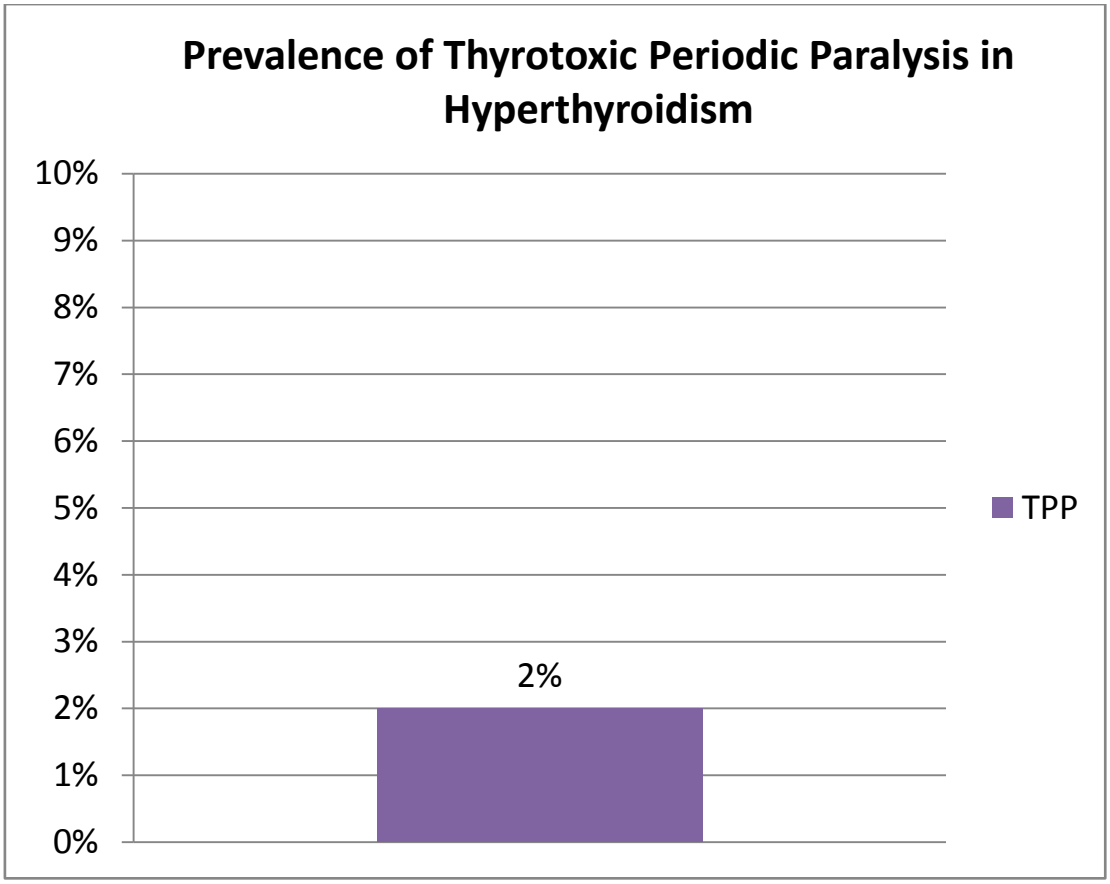
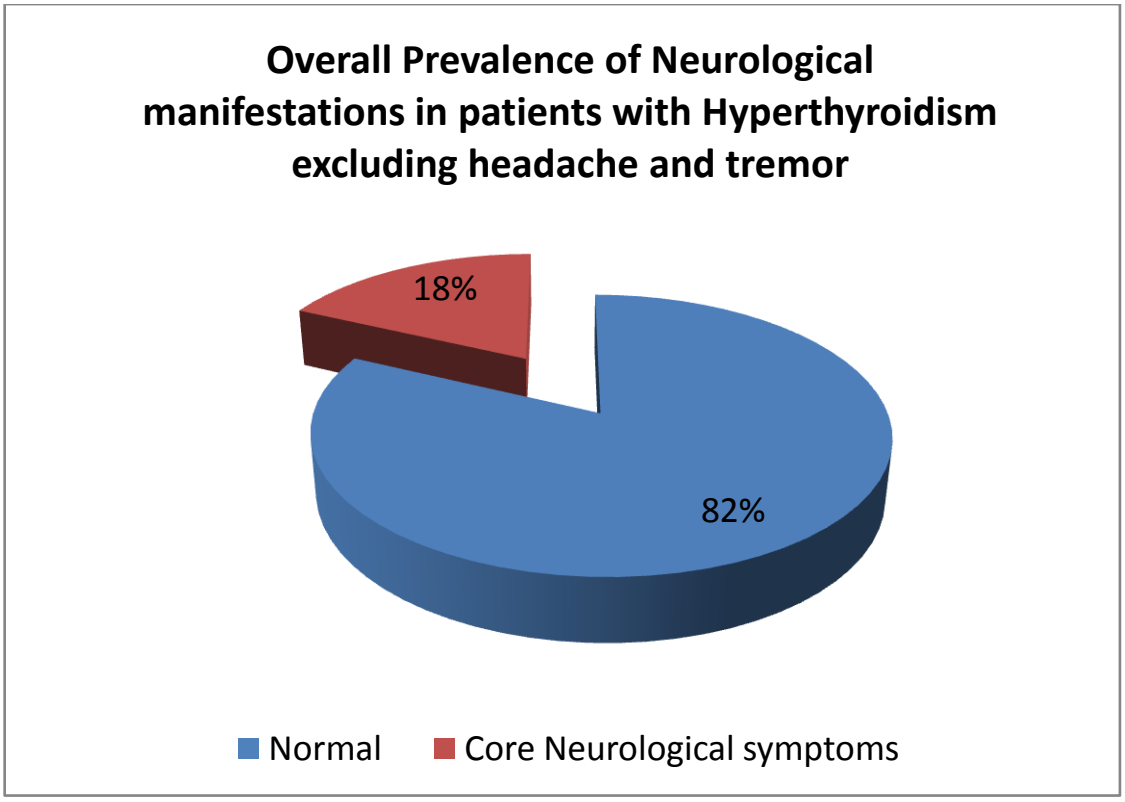
These patients presented with burning sensation over both feet with mild objective sensory loss over toes. The electrophysiology studies were normal for these patients. Hence the possibility of small fiber neuropathy was considered in these patients.



4% of patients had proximal muscle weakness associated with hyperthyroidism. One patient had generalized severe wasting in both upper and lower limbs associated with severe weakness. However CK value in these patients was normal. Electromyography in one of the patients was suggestive of myopathic weakness.



Only one male patient was diagnosed to have thyrotoxic periodic paralysis, even though there were lesser number of male hyperthyroid patients in our study group.

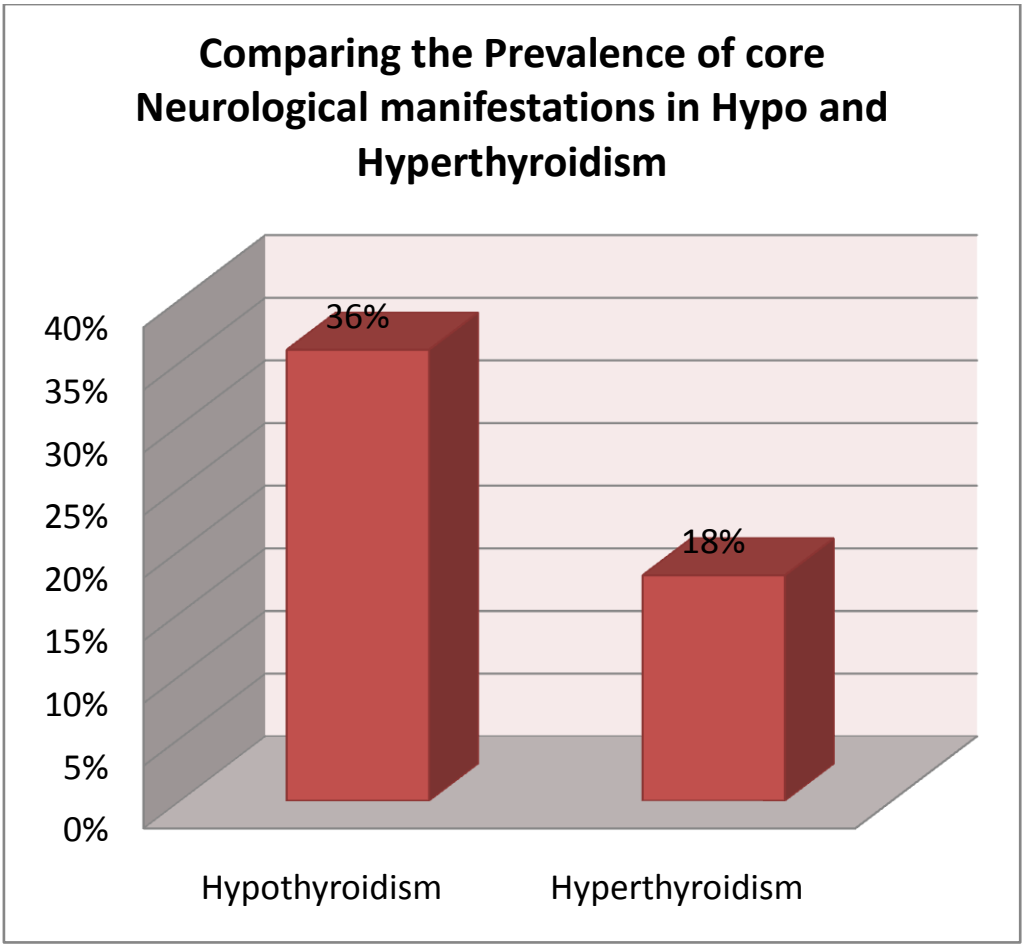


After excluding less serious form of the illness like tremor which is present in most hyperthyroid patients and other illness like headache where the association is mere a coincidence, the number of population having core neurological manifestations in our study is 18%

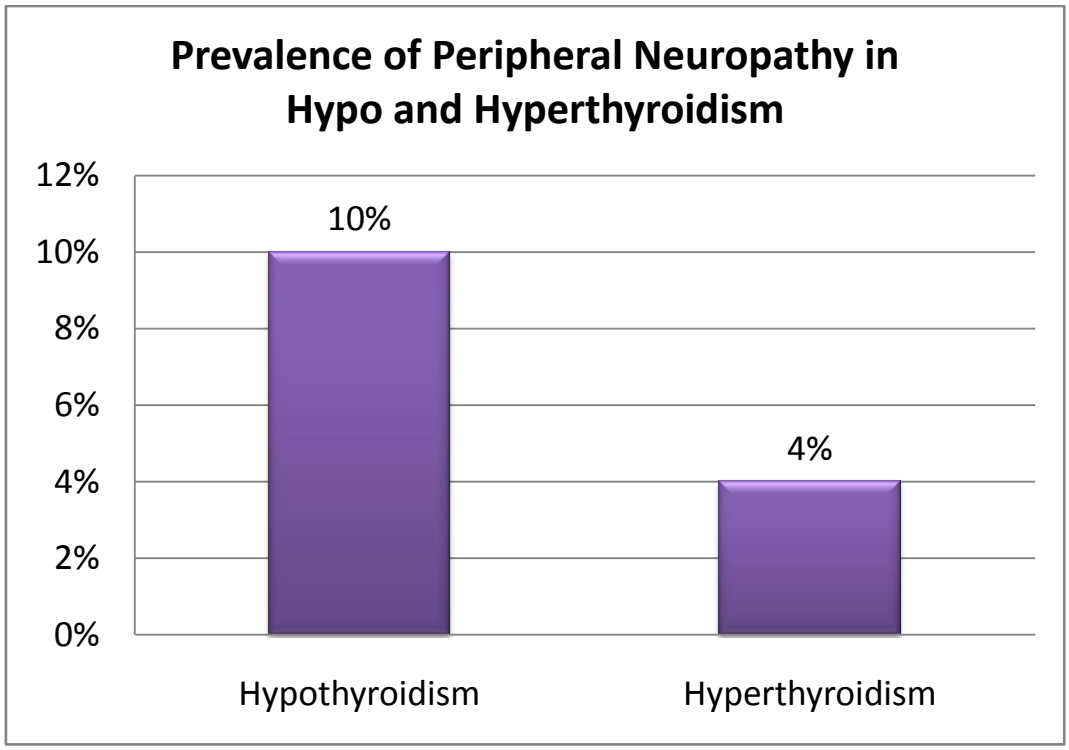
Comparing the prevalence of core neurological manifestation of Hypothyroidism and Hyperthyroidism

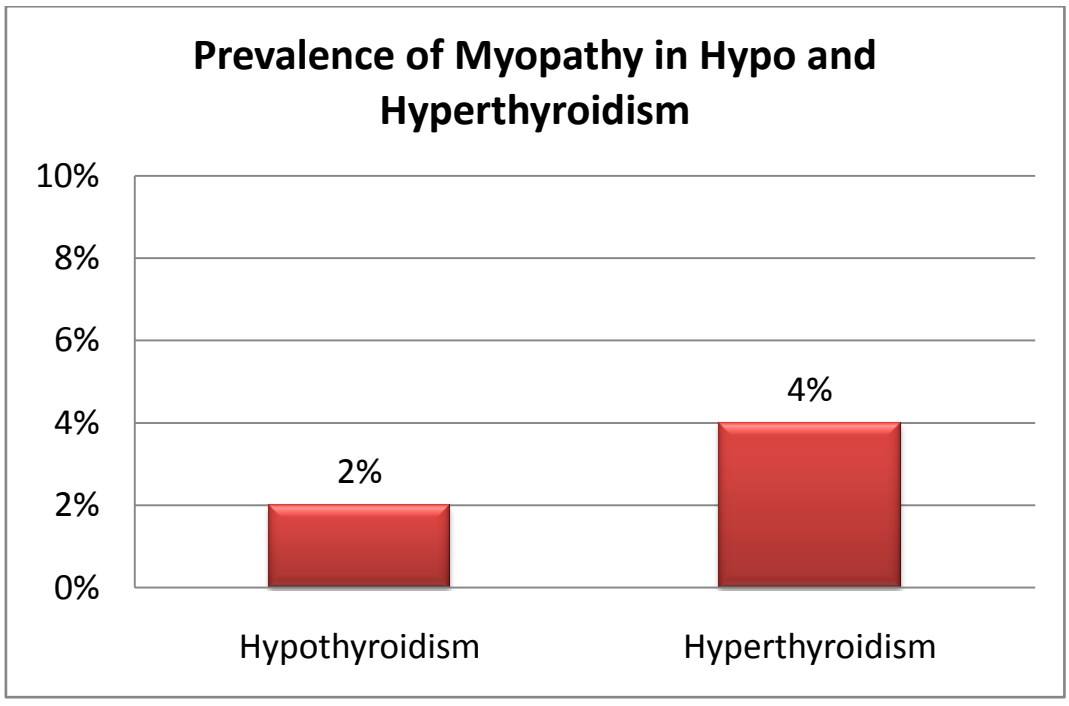
Core Neurological Manifestation		Group		Total	P value
		Hypothyroidism	Hyperthyroidism		
Yes	Count	18	9	27	0.043*
	% within Core Neurological Manifestation	66.7%	33.3%	100.0%	
	% within Group	36.0%	18.0%	27.0%	
No	Count	32	41	73	
	% within Core Neurological Manifestation	43.8%	56.2%	100.0%	
	% within Group	64.0%	82.0%	73.0%	
Total	Count	50	50	100	
	% within Core Neurological Manifestation	50.0%	50.0%	100.0%	
	% within Group	100.0%	100.0%	100.0%	

Note: * denotes significant at 5% level



The prevalence of core neurological manifestations in hypo and hyperthyroidism were compared in this study. The association of neurological manifestations more in hypothyroidism when compared to hyperthyroidism and is statistically significant at 5% confidence level.





Peripheral neuropathy is more common in hypothyroidism and myopathy is more common in hyperthyroid patients.

DISCUSSION

Neurological manifestations of hypothyroidism

Prevalence of overt and subclinical hypothyroidism

In our study group of 50 patients of hypothyroidism, most of patients 74% had overt hypothyroidism and 26% had sub clinical hypothyroidism. Those patients with elevated TSH and low levels of thyroxine are grouped under overt hypothyroidism and those with elevated TSH alone with normal levels of thyroxine are grouped under subclinical hypothyroidism.

Association of headache with hypothyroidism

On analyzing headache associated with thyroid dysfunction only 10% of patients had headache. The type of headache is episodic tension type headache. Globally, the percentages of the adult population with an active headache disorder are 46% for headache in general, 42% for tension-type headache, 11% for migraine and 3% for chronic daily headache[58]. In a large, population-based study of epidemiology of Tension-type Headache, the 1-year period prevalence were 38.3% for ETTH and 2.2% for CTTH[57].

The prevalence of tension type headache it is no greater than in the general population when compared to previous studies. The prevalence of headache is comparable to the general population and hence the association of headache cannot be attributed to hypothyroidism.

Prevalence of sleep disorders in hypothyroidism

8% of patients with hypothyroidism had sleep related problems. Most had increase in the duration of sleep. They feel sleepy and tired even though they had adequate sleep during night. One patient had sleep apnea causing poor sleep pattern in night time causing lethargy and somnolence during day time. Only one patient had insomnia.

Cognitive decline

8% of patients had minimal cognitive impairment on cognitive function assessment. Of these, in 4% of patient it is associated with encephalopathy features. Only the other 4% of cases had cognitive decline only. They have difficulty in learning and memory. They had impairment in higher cortical function, especially for executive function testing and recent memory impairment. These patients had long standing symptoms before starting treatment. Their symptoms showed only moderate improvement after thyroxine replacement. As said in the the review of literature the therapeutic window in reversing the central nervous system dysfunction is to initiate thyroxine supplementation with 5 to 7 months after the onset of symptoms. However frank dementia not occurred in our study population.

Hashimoto's Encephalopathy

Two of the patient in our study had encephalopathy associated with elevation of anti TPO antibodies. These patients had cognitive decline . One

patient had associated myeloneuropathy and the other had cerebellar involvement. Both patients showed improvement following treatment with injection methylprednisolone 1gm IV od for 5 days followed oral steroids. Hence the immune mediated mechanism affecting cerebrum and spinal cord in one patient and cerebrum and cerebellum in other patient can be considered.

Cerebellar involvement in a patient with hypothyroidism

There are two separate mechanisms resulting in cerebellar dysfunction in patients with thyroid disorders. One due to decrease in level and thus function of thyroxine itself and the other is immune mediated mechanism occurs irrespective of thyroid hormone levels .

In our patient it is associated with Hashimoto's encephalopathy. Hence immune mediated mechanism is the likely possibility. This patient symptoms improved slowly in a period of 3 months after treatment with IV methyl prednisolone 1 gram od followed by oral prednisolone . She also recieved thyroxine supplementation because of associated hypothyroidism.

Myelopathy associated with Hashimoto's encephalopathy - one of the rarest association[59,60]

39 year old female presented with cognitive decline, apathy, pyramidal involvement with brisk reflexes, extensor plantar and MRC power grading of 4 to 4+ in all four limbs. She also had symptoms and signs posterior column involvement and peripheral neuropathy. Etiological work up for other causes

were negative except for high anti TPO antibody titers and moderate elevation of TSH level with normal T_3,T_4 levels. Imaging shows non confluent periventricular T2 hyperintensities without any signal intensity changes in the cord. Hence the diagnosis of Hashimoto's encephalopathy with myeloneuropathy was made and was treated with injection methylprednisolone 1gram IV od for 5 days followed by oral prednisolone. Patient encephalopathy and myelopathy improved but peripheral neuropathy symptoms persisted.

The possible association of immune mediated mechanism for encephalopathy and myelopathy can be considered since these symptoms improved following immunosuppressive therapy with steroids. There is no improvement in peripheral neuropathy symptoms and hence long standing hypothyroid induced peripheral neuropathy can be considered.

Neuropathy

Entrapment neuropathy

10% of patients had sensory symptoms confined to upper limb. These patients nerve conduction study suggestive of carpal tunnel syndrome. There was no patients with symptoms of Tarsel Tunnel syndrome.

Peripheral neuropathy

10% of patient in our study had peripheral neuropathy. Of these 6% of patients had distal motor sensory neuropathy. Nerve conduction study of these patient showed axonal changes of both sensory and motor nerves

predominantly in lower limbs. In other 4% of patients had sensory symptoms confined to lower limbs only. Nerve conduction studies of these patients were normal. This probably attributes to small fiber neuropathy. It was also observed patients in overt hypothyroidism is more affected than in subclinical hypothyroidism.

Myopathy

Only 2% percent of patients in our study had complaints of proximal muscle weakness. MRC power grading shows only 4 to 4+ power in proximal muscles and distal muscle power were normal. There was no hypertrophy, wasting or fasiculations noted. Deep tendon reflexes showed delay in relaxation phase. Sensory symptoms examination were normal. Nerve conductions studies was normal. The CPK levels showed borderline elevation of 317U/L. This patient refuse to undergo EMG test.

Neurological manifestations of Hyperthyroidism

Association of headache with hyperthyroidism

On analyzing headache associated with hyperthyroidism only 16% of patients had headache. The type of headache is tension type headache and migraine. The prevalence of tension type headache it is no more greater than in general population when compared to previous studies[57]. The prevalence of headache is comparable to general population and hence the association of headache cannot be attributed to hyperthyroidism.

Prevalence of sleep disorders in hyperthyroidism

Patient with sleep disorders in hyperthyroidism is 8%. Almost all patients had insomnia in the form of unable to initiate sleep, unable to sustain sleep and getting up very early in the morning. This is probably related to the hyper metabolic state and anxiousness. This is associated with poor performance of day to day routine activities.

Incidence of tremor in patient with hyperthyroidism

Most patient with hyperthyroidism presents with tremulousness of hands. The tremor is more during posture and also in action. Because of this they have difficulty in carrying out skilled movements with hands. In our study, 74% of patients had tremor initially, which disappears with treatment as thyroxine level normalizes.

Myopathy

Only 4% percent of patients in our study has complaints of proximal muscle weakness. MRC power grading shows only 4- to 4 power in proximal muscles and distal muscle power were normal. There was no wasting or fasiculations noted. One patient showed brisk deep tendon reflex. Sensory system examination was normal. Nerve conductions studies and CPK levels were normal. Needle EMG examination features were suggestive of myopathy.

Peripheral neuropathy

4% of patient in our study had peripheral neuropathy. These patients presented with burning sensation over both foot and the sensory symptoms confined to lower limbs only. There is mild objective sensory loss of pain and temperature over the toes. Nerve conduction studies of these patients were normal. This probably attribute to small fiber neuropathy. There were no other co-morbid illness which could account for the same.

Thyrotoxic periodic paralysis

A male patient of age 22years presented as an emergency with acute onset weakness involving all four limbs. He had a past history of similar illness 1 year ago admitted and treated in another hospital. His investigation showed normal nerve conduction and hypokalemia. He was treated with IV potassium followed by oral syrup KCl. Further investigations showed thyrotoxicosis. Hence he was treated with antithyroid drugs and propranalol. Patient now on follow up for 1year without any recurrences.

In general the incidence of thyrotoxicosis in gender male:female ratio is 17:1 to 70:1. TPP was observed in a male patient with hyperthyroidism in our study. No females are affected by this disorder. Hence it is ideal to screen patients with thyroid function test presenting with hypokalemic periodic paralysis and at the most in males because of the more common association.

Comparing the neurological manifestation in hypo and hyperthyroidism

Overall neurological manifestation in hypo and hyperthyroidism

On comparing only the core neurological features associated with hypo and hyperthyroidism, the association is significantly high in hypothyroidism. This emphasis the need for assessing neurological manifestations in both groups but more importantly in hypothyroidism.

Comparing the association of peripheral neuropathy in hypo and hyperthyroidism

10% of patient in our study had peripheral neuropathy. Of these 6% of patients had distal motor sensory neuropathy. Nerve conduction study of these patient showed axonal changes of both sensory and motor nerves predominantly in lower limbs. Remaining 4% had small fiber neuropathy.

In contrast to this only 4% of patients with hyperthyroidism had symptoms confined to lower limb which is burning in nature. The nerve conduction study was normal in this patients. Hence the possibility of small fiber neuropathy is considered in this patient. Hence comparing the prevalence and severity of neuropathy it is less in hyperthyroidism when compared to hypothyroidism.

Comparing the association of myopathy in hypo and hyperthyroidism

4% patient in hyperthyroidism had myopathy in comparison only 2% had myopathy in hypothyroidism. There was significant wasting and more severe weakness in hyperthyroid patients. The serum CK is normal in both hyperthyroid patients where as it is elevated in hypothyroid patient. Hence it is well understood there is more chance of developing myopathy in hyperthyroidism and in affected patients it is more severe when compared to hypothyroidism

.

Neurological manifestations confined only to hypo and hyperthyroidism

Even though both hypo and hyperthyroidism had features in common there are specific symptoms which occurs only in one group. Carpal tunnel syndrome and cognitive decline were confined only to hypothyroidism. Tremor and TPP were confined only in hyperthyroidism. Hence when examining either hypo or hyperthyroidism it is ideal to look for specific neurological manifestations.

CONCLUSION

Neurological Manifestations in Hypothyroidism

The neurological manifestations observed in hypothyroidism were headache 12%, Sleep disorders 8%, cognitive decline 4%, Hashimoto's encephalopathy 4%, cerebellar involvement 2%, myeloneuropathy 2%, carpal tunnel syndrome 10%, peripheral neuropathy 10% and myopathy 2% .

It is observed from this study that hypothyroidism can affect almost the entire neuro axis like cerebrum, cerebellum, spinal cord, peripheral nerves and muscle . Hence it is essential to screen for thyroid function in patients with neurological manifestations.

Even though there are classical symptoms and signs associated with hypothyroidism, patient may present initially with neurological symptoms only. In this study, some of the patients with encephalopathy, peripheral neuropathy and myopathy presented without obvious symptoms of thyroid disorder.

It is important to consider immunological tests for thyroid, because treatment option may vary if it is abnormal. In our study two patients had encephalopathy, one with overt hypothyroidism and one with subclinical hypothyroidism (borderline elevation of TSH only). Immunological tests showed gross elevation of thyroid peroxidase antibody (TPO). Patients symptoms improved after being treated with steroids and thyroxine supplementation.

It is most essential to diagnose and start the treatment earlier for a better clinical outcome. In adult, hypothyroidism causes mild to moderate cognitive impairment which causes impairment of executive functions, learning abilities and memory that can be diagnosed only by doing higher mental system examination. In this study 4% of patients had cognitive decline associated with hypothyroidism and they were symptomatic for longer duration before the diagnosis of hypothyroidism was arrived. Since the treatment with thyroxine supplementation was delayed, they had residual cognitive impairment even after achieving euthyroid status.

There are certain neurological manifestations that are specific for hypothyroidism. In our study cognitive decline and carpal tunnel syndrome occurs exclusively in hypothyroidism. Hence it is essential to look for these neurological manifestations when examining hypothyroid patients.

Neurological Manifestations in Hyperthyroidism

The neurological manifestations observed in hyperthyroidism were tremor 74%, headache 16%, Sleep disorders 8%, peripheral neuropathy 4%, myopathy 4% and thyrotoxic periodic paralysis 2% .

Patient may present as an emergency masking the underlying hyperthyroid dysfunction and it is essential to screen for thyroid dysfunction because treatment options may vary depending upon the cause. In this study, one patient presented with second attack of hypokalemic periodic paralysis and on

work up found to have thyrotoxicosis. Hence diagnosed as thyrotoxic periodic paralysis and started on anti thyroid drugs. His hormone levels normalized and now on follow up without recurrence of periodic paralysis.

There are certain neurological manifestations that are more common for hyperthyroidism. Tremor is seen in most patient 74% with hyperthyroidism during the initial presentations which disappears with treatment once the thyroid hormone level normalizes.

There are certain neurological manifestations that are specific for hyperthyroidism. In our study tremor and thyrotoxic periodic paralysis occurred exclusively in hyperthyroidism.

Comparing the Neurological Manifestations in Hypo and Hyperthyroidism

Headache occurred in 12% of patients with hypothyroidism and 16% of patients with hyperthyroidism. The prevalence of headache it is no more greater than in general population when compared to previous studies. The occurrence of headache is comparable to general population and hence the association of headache cannot be attributed to hypo and hyperthyroidism.

Peripheral neuropathy occured in 10% of patients with hypothyroidism of which electrophysiology was suggestive of axonal changes in 6% of patients. In contrast only 4% of patients in hyperthyroidism had peripheral neuropathy which was suggestive of small fiber neuropathy where the nerve

conduction study was normal. Hence comparing the prevalence and severity of neuropathy it is less in hyperthyroidism when compared to hypothyroidism.

Myopathy occurred in 4% patient in hyperthyroidism in comparison only 2% in hypothyroidism. There was significant wasting and more severe weakness in hyperthyroid patients. Hyperthyroid patients has more chance of developing myopathy when compared to hypothyroid patients.

The serum CK is normal in both hyperthyroid patients where as it is elevated in hypothyroid patients. The serum CK is typically normal in hyperthyroidism where as it is elevated in hypothyroidism. Hence screening with serum CK does not rules out hyperthyroid myopathy.

On comparing only the core neurological features associated with hypo and hyperthyroidism, the association is significantly high in hypothyroidism.

Thyroid disorders can affect the entire neuro axis and may present with neurological manifestations without specific symptoms and signs of thyroid dysfunction. This emphasis the need for thyroid function testing in patients presenting with neurological symptoms even without classical thyroid symptoms.

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PROFORMA

Neurological manifestations in thyroid disorders

Name- Age/Sex- OP/IP No-

Phone No-

TSH - Diffuse/nodular goiter-

Total/FreeT3 - USG-

Total/FreeT4 - TPO antibody-

Other illness-

Diagnosis- Duration of illness-

Complaints- Treatment-

Specific symptoms-

Neurological manifestations

Symptoms	**Signs**
Headache Anxiety Insomnia Sleepiness Depression Delirium Psychosis Disorientation Seizures CN involvement Weakness Sensory Ataxia Tremor	HMF- CN- Motor- Sensory- Cerebellum- EPS-

NCS

Motor	latency	amlitude	CV	F-wave
R-median				
L-median				
R-ulnar				
L-ulnar				
R-peroneal				
L-peroneal				
R-tibial				
L-tibial				

Sensory	latency	amlitude	CV
R-median			
L-median			
R-ulnar			
L-ulnar			
R-sural			
L-sural			

Other investigations:

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI -3

Telephone No : 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr.A.Marian Jude Vijay
PG in Neurology
Madras Medical College, Chennai -3

Dear Dr.A.Marian Jude Vijay,

The Institutional Ethics committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled " A study on neurological manifestations in thyroid disorders" No.21112012.

The following members of Ethics Committee were present in the meeting held on 01.11.2012 conducted at Madras Medical College, Chennai -3.

1. Prof. R. Nandhini MD -- Member Secretary
   Director, Instt. of Pharmacology ,MMC, Ch-3
2. Prof. Reghu MD -- Member
   Director , Inst. Of Internal Medicine, MMC, Ch-3
3. Prof. Shyamraj MD -- Member
   Director i/c , Instt. of Biochemistry , MMC, Ch-3
4. Prof. P. Karkuzhali. MD -- Member
   Prof., Instt. of Pathology, MMC, Ch-3
5. Prof. G.Muralidharan MS -- Member
   Prof of Surgery, MMC, Ch-3
6. Thiru. S. Govindsamy. BA, BL -- Lawyer

We approve the proposal to be conducted in its presented form.

Sd/ Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

R Nandini 19/11/12
Member Secretary, Ethics Committee

Information sheet

- We are conducting a study of the **"Neurological manifestions in patients with thyroid disorders "** at the Institute of Neurology, Rajiv Gandhi Govt. General Hospital, Chennai. The purpose of this study is to analyse the use of antiepileptic drug combinations in patients with epilepsy and its rationality with regard to seizure type, seizure control, drug interactions and adverse effects.

- The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

- Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time. Your decision will not result in any loss of benefits to which you are otherwise entitled.

- The results of the study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of the investigator **Signature of the participant**

Date:

PATIENT CONSENT FORM

Study Details : **"A Study on Neurological Manifestations in Thyroid Disorders"**

Study Centre : **Institute of Neurology,**
Madras Medical College and
Rajiv Gandhi Government General Hospital,
Chennai - 600 003.

Patient may check (✓) these boxes:

I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction. ☐

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. ☐

I understand that the investigator of the clinical study, others working on his behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ☐

I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms. ☐

I hereby give permission to undergo complete clinical examination and diagnostic tests including hematological, biochemical, radiological, EMG, EEG, NCS, Lumbar puncture and muscle biopsy, appropriate to the clinical diagnosis. ☐

I hereby consent to participate in this study. ☐

Signature / Thumb impression: Place : Date :

Patient Name and Address:

Signature of Investigator: Place : Date :

Study Investigator's Name :

MASTER CHART (HYPOTHYROIDISM)

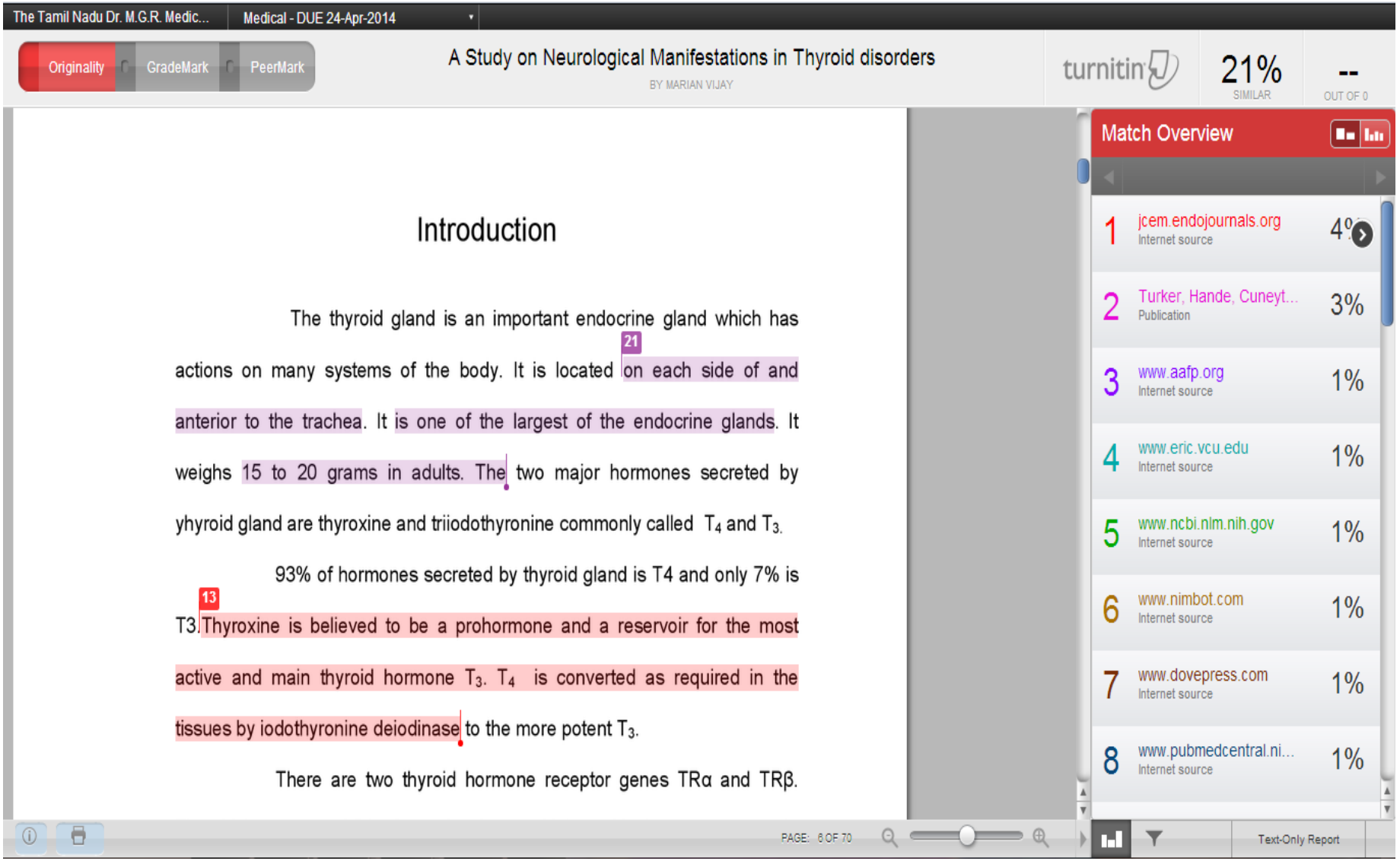
S.NO	NAME	AGE	SEX	TSH	T4	T3	HEADACHE	SEIZURE	ENCEPHALOPATHY	INSOMNIA	SLEEPINESS	PSYCOSIS	DELIRIUM	DEPRESSION	COGNITIVE DECLINE	CN INVOLVEMENT	MYOPATHY	ENTRAPMENT NEUROPATHY	PERIPHERAL NEUROPATHY	ATAXIA	STROKE	COMA	MYELOPATHY
1	Manonmani	50	F	148	low	low													yes				
2	Sammanthiammal	56	F	29.1	low	low													yes				
3	Sheela	14	F	46.2	low	low									yes								
4	Thilakavathy	49	F	27.2	low	low																	
5	Savithri	39	F	34	low	low					yes							CTS					
6	Kanchana	38	F	16.2	low	low				yes													
7	Baby	35	F	83.65	low	low	yes																
8	Muniammal	40	F	8.5	low	N			yes						yes					yes			
9	Lakshmi	35	F	11.1	low	low	yes																
10	Rathnakumari	24	F	6.43	N	N																	
11	Angel	37	F	13.14	N	low																	
12	Amutha	23	F	7.5	N	N																	
13	Hamsa	27	F	7.2	N	N	yes																
14	Sasikala	19	F	5.77	low	low																	
15	Jegadesan	35	M	17.4	low	low	yes				yes												
16	Sumathy	44	F	7.5	low	low																	
17	Hemavathy	24	F	25	low	low																	
18	Kamala	43	F	7	low	low																	
19	Sumathy	32	F	60.77	low	low												CTS					
20	Rajakumari	45	F	7	N	N												CTS					

21	Sivaranjani	21	F	25	low	low													yes				
22	Shanthi	30	F	6.5	N	N					yes												
23	Gilda	28	F	7.74	N	N																	
24	Sumathy	25	F	6.5	N	N																	
25	Jeyanthi	31	F	6.5	N	N																	
26	Ponkodi	44	F	100	N	low																	
27	Suriya	39	F	11.4	N	N			yes						yes				yes				yes
28	Jamuna	44	F	7.9	low	low																	
29	Kumari	36	F	21.5	low	low												CTS					
30	Parvathy	40	F	11.5	low	low																	
31	Chinna pappa	30	F	6	low	N								yes									
32	Mariammal	60	F	5.7	low	N								yes									
33	Ponniammal	24	F	9.6	N	N																	
34	Girija	40	F	12.2	low	low	yes											CTS					
35	Saroja	72	F	7.5	N	N																	
36	Rajeswari	40	F	8.5	low	low																	
37	Stella	28	F	100	low	low																	
38	Vijaya	39	F	11	low	low																	
39	Chelladurai	28	M	19.2	low	low									yes								
40	Thangaraj	48	M	150	low	low																	
41	Mala	36	F	88.25	low	low	yes																
42	Kattammal	60	F	15.4	N	low													yes				
43	Meenakshi	21	F	8.32	N	N																	
44	Sasikala	39	F	7.5	N	N																	
45	Sivakami	30	F	48.78	low	low																	
46	Parimala	38	F	7.63	N	N																	
47	Tharasundari	55	F	12.8	low	low											yes						
48	Senthilnathan	37	M	14.4	low	low																	
49	Shakila	25	F	150	low	low																	
50	Sivakami	15	F	150	low	low																	

MASTER CHART (HYPERTHYROIDISM)

S. NO	NAME	AGE	SEX	TSH	T4	T3	HEADACHE	SEIZURE	ENCEPHALOPATHY	INSOMNIA	SLEEPINESS	PSYCOSIS	DELIRIUM	DEPRESSION	COGNITIVE DECLINE	EXOPTHALMAS	CN INVOLVEMENT	TREMOR	MYOPATHY	TPP	PERIPHERAL NEUROPATHY	ATAXIA	MYASTHENIA GRAVIS
1	Vijaya	40	F	0.01	high	high	yes																
2	Saravanan	25	M	0.01	high	high																	
3	Valli	40	F	0.33	high	N																	
4	Roja	18	F	0.03	high	high												yes					
5	Pushpa	42	F	0.01	high	high												yes					
6	Sumathy	25	F	0.02	high	high										yes		yes					
7	Kala	42	F	0.031	high	high												yes			yes		
8	Baskar	46	M	0.04	high	high										yes		yes					
9	Lekha	22	F	0.013	high	high	yes			yes													
10	Savithri	45	F	0.2	high	high												yes					
11	Lalitha	34	F	0.1	high	high												yes					
12	Lakshmi	32	F	0.18	high	high										yes		yes					
13	Poorani	40	F	0.02	high	high												yes					
14	Mallika	30	F	0.01	high	high										yes		yes					
15	Rajan	33	M	0.05	high	high				yes								yes					
16	Ezhil	40	F	0.2	high	high										yes		yes					
17	Jeyamani	34	F	0.06	high	high	yes											yes	yes				
18	Muthuselvi	32	F	0.1	high	high												yes					
19	Vellammal	41	F	0.01	high	high												yes			yes		
20	Chandra	27	F	0.12	high	high																	
21	Prema	32	F	0.05	high	high																	
22	Parvathy	38	F	0.15	high	high										yes		yes	yes				
23	Sundari	28	F	0.02	high	N												yes					
24	Akalya	19	F	0.12	high	high	yes											yes					
25	Meenakshi	34	F	0.15	high	high				yes								yes					

S. NO	NAME	AGE	SEX	TSH	T4	T3	HEADACHE	SEIZURE	ENCEPHALOPATHY	INSOMNIA	SLEEPINESS	PSYCOSIS	DELIRIUM	DEPRESSION	COGNITIVE DECLINE	EXOPTHALMAS	CN INVOLVEMENT	TREMOR	MYOPATHY	TPP	PERIPHERAL NEUROPATHY	ATAXIA	MYASTHENIA GRAVIS
26	Ramesh	27	M	0.05	high	high																	
27	Poonkodi	32	F	0.18	high	high	yes									yes		yes					
28	Thulasi	43	F	0.05	high	N	yes											yes					
29	Selvi	35	F	0.12	high	high												yes					
30	Subammal	39	F	0.15	high	high												yes					
31	Balakanna	29	M	0.06	high	high												yes					
32	Amutha	38	F	0.18	high	high												yes					
33	Vikram	29	M	0.11	N	high										yes		yes					
34	Thilakavathy	40	F	0.06	high	high	yes			yes													
35	Jeyalaksmi	37	F	0.14	high	high																	
36	Hemalatha	31	F	0.09	high	high												yes					
37	Manonmani	37	F	0.2	high	high																	
38	Sivashankari	34	F	0.08	high	high										yes		yes					
39	Uma	29	F	0.15	high	high												yes					
40	Karthik	38	M	0.05	high	high												yes					
41	Priyadharshini	25	F	0.1	high	N												yes					
42	Rajesh	22	M	0.01	high	high										yes		yes		yes			
43	Shanthi	27	F	0.13	high	high																	
44	Thenmozhi	39	F	0.08	high	high												yes					
45	Lalitha	41	F	0.13	high	high																	
46	Suganthi	30	F	0.06	high	high	yes																
47	Deepa	23	F	0.058	high	high												yes					
48	Revathy	34	F	0.14	high	high												yes					
49	Sharadha	23	F	0.08	high	high										yes		yes					
50	Bhuvaneswari	29	F	0.014	high	high												yes					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A Study on Neurological Manifestations in Thyroid disorders
BY MARIAN VIJAY
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Introduction
The thyroid gland is an important endocrine gland which has actions on many systems of the body. It is located on each side of and anterior to the trachea. It is one of the largest of the endocrine glands. It weighs 15 to 20 grams in adults. The two major hormones secreted by yhyroid gland are thyroxine and triiodothyronine commonly called T_4 and T_3.
93% of hormones secreted by thyroid gland is T4 and only 7% is T3. Thyroxine is believed to be a prohormone and a reservoir for the most active and main thyroid hormone T_3. T_4 is converted as required in the tissues by iodothyronine deiodinase to the more potent T_3.
There are two thyroid hormone receptor genes TRα and TRβ.
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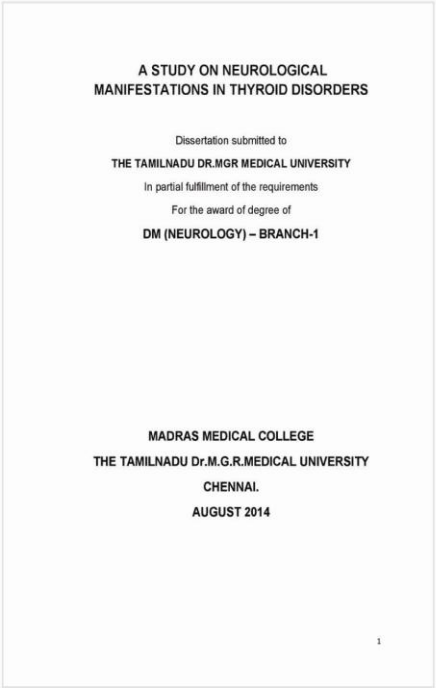

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